“STUDY OF SIGNIFICANCE OF ECHOCARDIOGRAPHY IN THALASSEMIA MAJOR / INTERMEDIA PATIENTS AT TERTIARY CARE CENTRE”, ICH&HC, CHENNAI.

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CERTIFICATE

This is to certify that dissertation entitled **"STUDY OF SIGNIFICANCE OF ECHOCARDIOGRAPHY IN THALASSEMIA MAJOR / INTERMEDIA PATIENTS AT TERTIARY CARE CENTRE", ICH&HC, CHENNAI** submitted by DR. USHA. B.K to the faculty of paediatrics, The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the requirement for the award of M.D. Degree (Paediatrics) is a bonafide research work carried out by her under direct supervision and guidance.

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DECLARATION

I Dr. Usha B. K. solemnly declared that the dissertation entitled **"STUDY OF SIGNIFICANCE OF ECHOCARDIOGRAPHY IN THALASSEMIA MAJOR / INTERMEDIA PATIENTS AT TERTIARY CARE CENTRE", ICH&HC, CHENNAI** has been prepared by me. This is submitted to the Tamilnadu Dr . M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulations for the M.D degree examination in paediatrics.

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PLACE :

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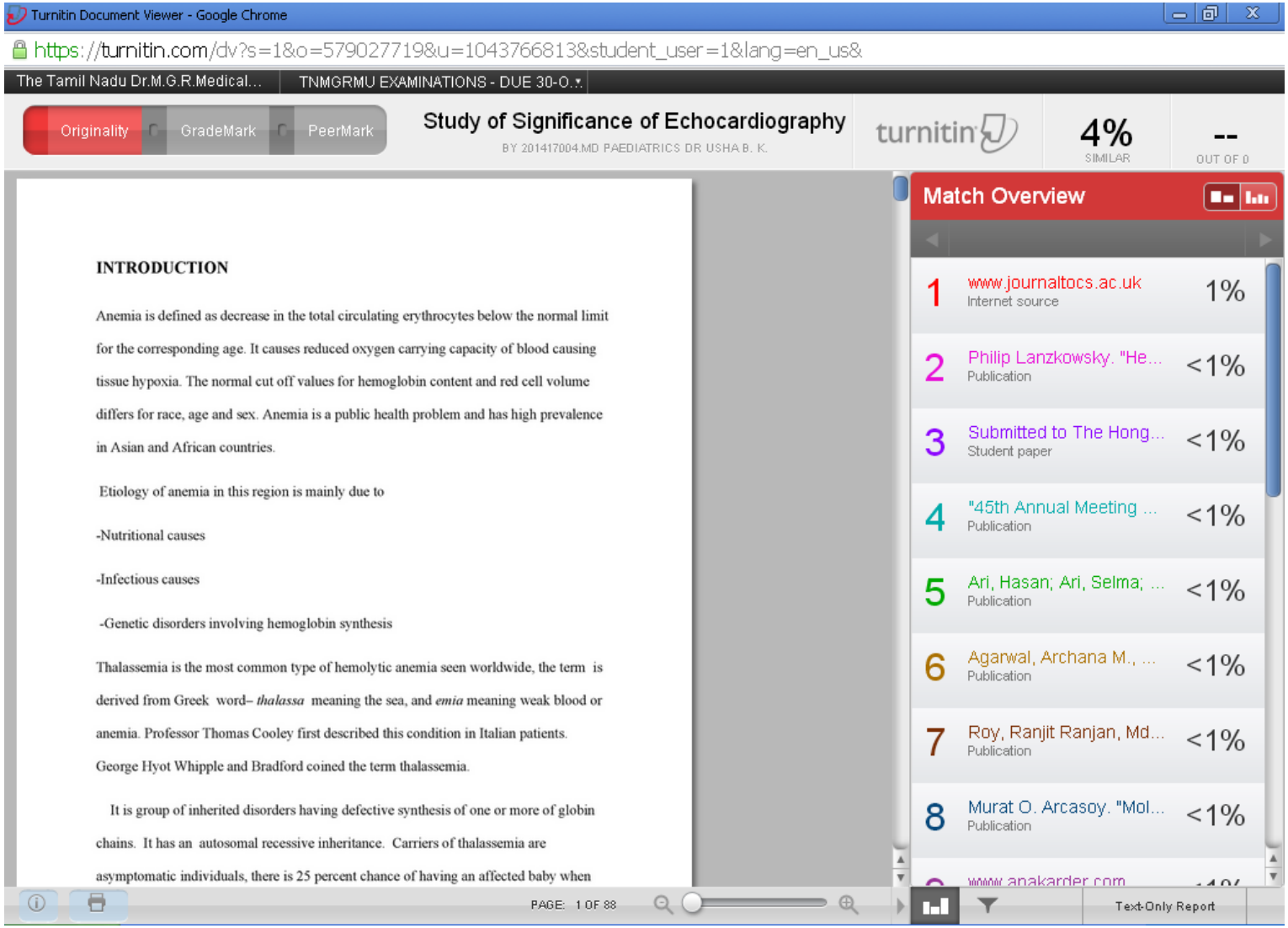
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INTRODUCTION
Anemia is defined as decrease in the total circulating erythrocytes below the normal limit for the corresponding age. It causes reduced oxygen carrying capacity of blood causing tissue hypoxia. The normal cut off values for hemoglobin content and red cell volume differs for race, age and sex. Anemia is a public health problem and has high prevalence in Asian and African countries.
Etiology of anemia in this region is mainly due to
-Nutritional causes
-Infectious causes
-Genetic disorders involving hemoglobin synthesis
Thalassemia is the most common type of hemolytic anemia seen worldwide, the term is derived from Greek word– thalassa meaning the sea, and emia meaning weak blood or anemia. Professor Thomas Cooley first described this condition in Italian patients. George Hyot Whipple and Bradford coined the term thalassemia.
It is group of inherited disorders having defective synthesis of one or more of globin chains. It has an autosomal recessive inheritance. Carriers of thalassemia are asymptomatic individuals, there is 25 percent chance of having an affected baby when
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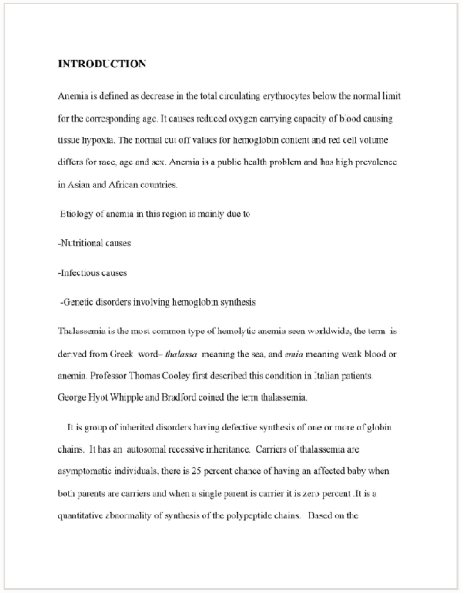

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It is group of inherited disorders having defective synthesis of one or more of globin chains. It has an autosomal recessive inheritance. Carriers of thalassemia are asymptomatic individuals, there is 25 percent chance of having an affected baby when both parents are carriers and when a single parent is carrier it is zero percent .It is a quantitative abnormality of synthesis of the polypeptide chains. Based on the

CONTENTS

“Study of significance of echocardiography in thalassemia major/intermedia patients at tertiary care centre”ICh&HC, Chennai.

Usha B K*, Ravichandran T. Gnanasambandam S.

AIM OF THE STUDY:

To study the cardiovascular complications in transfusion dependent beta thalassemia major/intermedia patients and to establish the significance of echocardiography in them.

MATERIALS & METHODS

This descriptive study was done on transfusion dependent thalassemia major / intermedia patients in the age group of 2 to 12 years on regular chelation therapy coming to ICH and HC, Chennai. Patients with a known congenital heart disease or terminal illness were excluded.

A detailed history including symptoms, age at diagnosis, consanguinity, sibling history was taken. Blood for complete blood count and serum ferritin was taken and patients were subjected to electrocardiography, 2D and M-mode echocardiography and continous wave Doppler.

Patients were divided into two groups based on Hb electrophoresis into TM and TI .The ecg and echocardiographic findings of these patients were compared. Patients were further categorized on serum ferritin values as those with >1000ng/dl and <1000ng/dl and it was studied with ecg and echocardiographic findings

RESULTS:

24 %(n=13) thalassemia patients have pulmonary hypertension. Incidence of pulmonary hypertension was high in TI(42%) than TM(21%) in our study. LV mass and LV mass index was increased in 63% of patients. Serum ferritin values did not correlate with the LVmass/m^2, pulmonary hypertension and cardiac dysfunction on echocardiography.

QT_c was normal and arrhythmias was not seen on ecg in our study.

CONCLUSIONS:

Echocardiography can be used as screening tool in asymptomatic thalassemia patients. Serum ferritin is not a good indicator of cardiac toxicity secondary to iron. Cardiac MRI is the gold standard for detection of cardiac iron load.

RECOMMENDATIONS: Echocardiography can be used as a screening tool and periodic follow up for cardiac complications in thalassemia patients.

Key words: thalassemia major, intermedia, echocardiography,

INTRODUCTION

Anemia is defined as decrease in the total circulating erythrocytes below the normal limit for the corresponding age. It causes reduced oxygen carrying capacity of blood causing tissue hypoxia[8,16]. The normal cut off values for hemoglobin content and red cell volume differs for race, age and sex. Anemia is a public health problem and has high prevalence in Asian and African countries[5].

Etiology of anemia in this region is mainly due to[3]

- Nutritional causes
- Infectious causes
- Genetic disorders involving hemoglobin synthesis

Thalassemia is the most common type of hemolytic anemia seen worldwide, the term is derived from Greek word– *thalassa* meaning the sea, and *emia* meaning weak blood or anemia. Professor Thomas Cooley first described this condition in Italian patients. George Hyot Whipple and Bradford coined the term thalassemia[51].

It is group of inherited disorders having defective synthesis of one or more of globin chains. It has an autosomal recessive inheritance. Carriers of thalassemia are asymptomatic individuals[4], there is 25 percent chance of having an affected baby when both parents are carriers and when a single parent is carrier it is zero percent .It is a quantitative abnormality of synthesis of the

polypeptide chains. Based on the impairment of the globin chain, thalassemia is classified as alpha or beta thalassemia respectively

EPIDEMIOLOGY:

As per WHO, 7 percent of world's population are estimated to be carriers of hemoglobinopathies[5]. It is the most common single gene disorder found worldwide affecting millions of human beings, more commonly in malaria endemic region. Prevalence of monogenic disorders globally is 10/1000.

Alleles of thalassemias are carried by 3 % of the world`s population[5,16]. And in South East Asia alone 5 to 10 % of abnormal alleles are carried for alpha thalassemias . Alpha thalassemia is seen most commonly in China and South East Asia and less frequently in Kuwait, Middle east, Northern Europe, Italy and India where β thalassemia is more[8]. Immigration and marriage

between communities has lead to the spread of thalassemia even in European and American countries which are not endemic for malaria.

About 50,000 to 100,000 children in middle and low income countries die every year with thalassemia major.

THALASSEMIA IN INDIA:

In India the burden of this disease is high with about 12,000 babies born with thalassemia major each year. Carrier rate is 1 to 17 %(average is 3.2%). Distribution varies in different parts of the country. Prevalence is high in Punjab, Sindhis in north India[4,7].

Though a preventable disease, the financial burden of blood transfusions, mortality and morbidity associated with the disorder is high. Cardiac complications are the most common cause of death in thalassemia patients. Without management by blood transfusions, these children usually die in the first few years of life. They develop severe anemia and hyperdynamic circulation, followed by congestive cardiac failure and death. Before the advent of iron chelation therapy chronic severe anemia and iron over load were the primary causes for cardiomyopathy and mortality in thalassemia patients. Increased incidence of pulmonary hypertension and arrhythmia is seen in these patients compared to the general population[11]. With the introduction of blood transfusions and chelation therapy the morbidity and deaths have been pushed a decade later. The survival and life expectancy has improved[32].

Clinically, it is difficult to diagnose symptoms of heart failure as they overlap with the symptoms of pre existing anemia. Many symptoms that are seen in anemia like increased heart rate, easy fatiguability, exertional dyspnoea, liver enlargement are also seen in heart failure. Hence these patients need continuous monitoring of symptoms and signs aided with investigations for early detection of complications and its management for better outcome.

To detect this pre symptomatic stage of cardiac complications many techniques are available in India like electrocardiogram, echocardiography, T2 cardiac MRI, MUGA scanning. Ecg and echocardiography are cost effective, non invasive and easily available in many parts of the country. However the gold standard to assess the cardiac iron overload is by magnetic resonance imaging which is expensive, time consuming and requires highly skilled personnel for the procedure.

Hence many studies are done to know the sensitivity and specificity of these two investigations in detecting early cardiac involvement in thalassemia patients. The goal is to have an investigation tool which is less expensive, easily available and can also give accurate results.

Thalassemia is a group of genetic disorder with defective globin chain synthesis. It is characterized by varying degrees of ineffective erythropoesis. Mutations of β – globin genes occur predominantly in children of Mediterranean , Southern, and Southeast Asian ancestry[16]. Clinically thalassemia is classified into α and β thalassemias, each with varying degrees of α and β chains mutated. Abnormality in beta globin chain synthesis causes β

thalassemia due to point mutations in one or two of the beta globin genes. Though more than 60 beta thalassemia mutations are seen in our country, only five types(IVS 1-5,619-bp deletion, IVS 1-1. FS8/9, FS41/42) account for majority of the cases[4].

To know the pathophysiology of anemia in thalaseemia and iron overload an overview of hemoglobin synthesis and iron metabolism is necessary.

SYNTHESIS OF HAEMOGLOBIN

Adult hemoglobin is made of two α and two β chains. Thalassemia is due to the failure in switching over from fetal to adult hemoglobin resulting in excessive fetal hemoglobin and low levels of hemoglobin A along with A2[19].

Synthesis of hemoglobin starts in pro erythroblasts and proceeds to reticulocyte phase of erythrocytes. A pyrrole molecule is formed after succinyl CoA binds with glycine. 4 pyrroles join to give protoporphyrin IX. Heme molecule is formed once protoporphyrin IX combines with iron. This heme now combines with polypeptide to form either a α or β chain. 2 α and 2 β chain constitute a tetramer of hemoglobin A molecule. α chain is made up of 141 AA & β chain is made up of 146 AA. Molecular weight of each chain is about 16,000. Molecular weight of hemoglobin A is 64,458.

Based on amino acid in the polypeptide part of hemoglobin , there are 4 types of globins chains alpha, beta, gamma , delta chains.

One molecule of haemoglobin carries eight oxygen atoms , each iron atom binds with 2 atoms of oxygen. This is important as the oxygen binding capacity of haemoglobin is dependent on the type of globin chain it contains. Molecular oxygen binds loosely and reversibly with iron so that, it is released at tissue capillaries.

GENETICS

- Pseudo genes which are inactive are implicated in the pathogenesis of thalassemia.α and β globin genes are located on the short arm of 16 and 11 chromosome respectively.
- Following functional genes, ε, γ, Aγ, δ and β are seen in β-like cluster. They are arranged in 5' to 3'.
- Embryonic E gene codes for Hb Gower1 and Hb Gower 2.
- Delta globin gene which codes for Hb A2 differs only in 10 residues in comparison with β -globin gene.
- Adult Hb comprises of two 2α and 2β globin chains.
- Fetal hemoglobin synthesis starts when erythropoeisis occurs in liver during fetal life.
- When erythropoeisis switch occurs from liver in fetal life to bone marrow at about 20wks of gestation, there will be transition in production of Hb F to Hb A.

However this switch is related to time of gestation rather than site of erythropoeisis[8,16,18].

MOLECULAR PATHOGENESIS

Clinical syndrome	Genotype	Molecular genetics
B- Thalassemia major	Homozygous β-thalassemia (β^0/β^0, β^+/β^+, $\beta^0\beta^+$)	Point mutations cause abnormalities in transcription splicing or translation of B- globin mRMA
B- Thalassemia intermedia	Variable (β^0/β^+ ,β^+/β^+ ,β^0/β^+, β^+/β)	Point mutations cause abnormalities in transcription splicing or translation of B- globin mRNA
B- Thalaseemia minor	Heterozygous β-Thalassemia β^0/β, β^+/β	
α Thalaseemia		
Hydrops fetalis	-/- -/-	Gene deletions
HbH disease	-/- -/α	Gene deletions
α thalassemia trait	-/- α/α, -/α, -/α	Gene deletions
Genetic Classification of Thalassemias[16]		

β- thalassemia is due to mutation which decreases the production of β – globin chains. The clinical picture varies secondary to the heterogeneity of mutation, that can be β^o mutation or β^+ mutation[18].

β^o – total absence of β-globin chains

β^+ decreased amount β-globin chains

Though over hundreds of causative mutations are implemented in β-thalaseemia, few important ones are mentioned here[16].

- Splicing mutations:- mostly seen in β+ thalaseemia, predominantly in introns when there is partial absence of β globins. In βo thalassemia, the mutations completely stop the normal β-globin mRNA production since they destroy normal splice functions in the RNA.
- Promoter region mutations:- β+ that are mostly associated with these mutations. Here the transcription is decreased by 80%.
- Chain terminator type of mutations seen mostly associated with βo thalassemia.

Two types of mutations [(i) introduction of new stop codon in exons, (ii) frameshift mutation within the exons occur to block translation leading to absence of β-globin chains.

FATE OF RBC

Life span of erythrocytes is 120 days. RBCs contain enzymes which maintain

- transport of ions.
- pliability of erythrocyte membrane
- iron in ferrous form and proteins unoxidised.

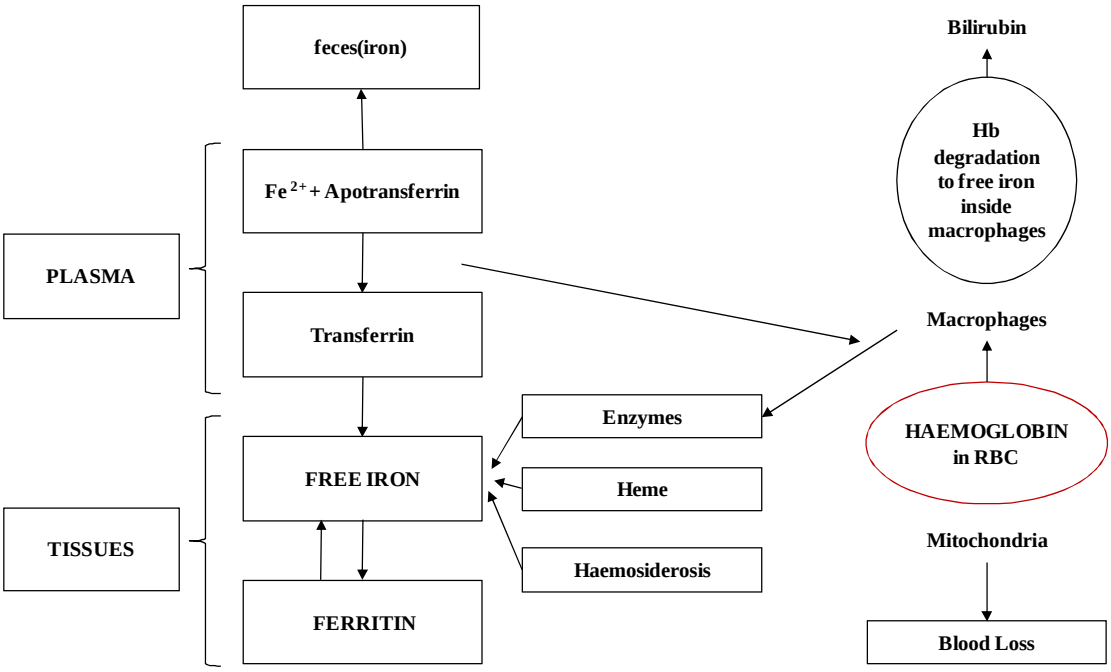
Fragile red blood cells breakdown while passing through spleen and release hemoglobin which is phagocytosed mostly by liver, spleen and bone

marrow, where macrophages release iron. This free iron is carried by the transport protein transferrin for production of new erythrocytes or converted into storage form ferritin in liver, cardiac and other sites.. Bilirubin form biliverdin is secreted through bile.

IRON METABOLISM

Total amount of iron in human body is about 4 to 5 grams of which 65 percent is hemoglobin, and myoglobin is 4 percent, 0-1percent combines with transferrin and 30 percent is in the storage form ferritin in liver, spleen[19].

TRANSPORT AND STORAGE OF IRON



Iron absorption:

Iron metabolism is unique. The absorption of iron plays a major role and excretion of iron has minor role to maintain iron balance. There is no mechanism for excretion of iron other than desquamation of epithelial cells from skin, intestine and urinary tract. Menstruation and pregnancy is a major cause of loss of iron in females.

About 5 % to 10 % (0.5 to 1mg) of the dietary iron is absorbed from the body. This can increase to as high as 20 % in state of iron deficiency that is equal to 3 to 4 mg per day. Heme iron is better absorbed than non heme iron. And presence of heme iron increases absorption of non heme iron.

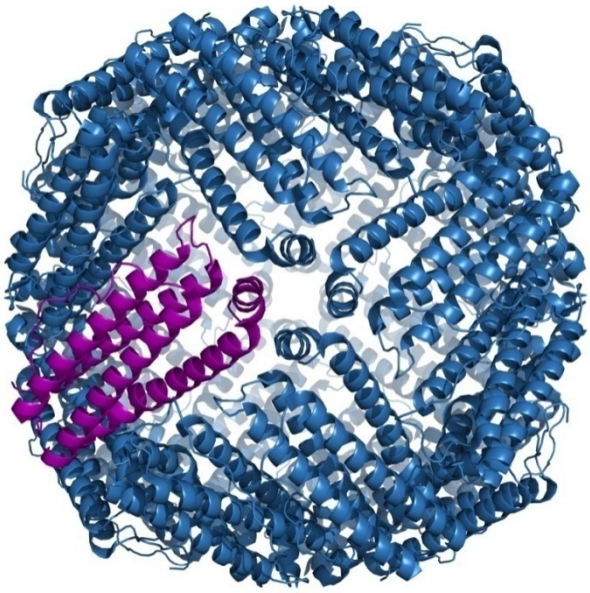
Iron is absorbed in the small intestine mainly in proximal duodenum. Ferrous form is better absorbed than ferric form. Gastric acid enhances the absorption of iron. Heme iron is absorbed more efficiently than inorganic iron, independent of duodenal pH. There are number of factors which influence iron absorption from the instestine. After iron enters the intestine it can be retained inside the cell and lost once enterocyte is sloughed or transported across the basolateral membrane to enter the body. Iron retained in the enterocyte will be incorporated into ferritin.

Inside the cell, iron binds to unidentified carrier molecule which assist in delivery to various intracellular locations, such as mitochondria (heme synthesis) and ferritin (for storage). Iron in transit in the cell at any point of time is small. This minute pool of transit iron, is in the Fe^{2+} form, is

biologically active and considered to be potentially toxic form. Iron stored in ferritin and hemosiderin , is nontoxic and metabolically inactive.

Iron is stored inside the body by binding with the ubiquitous cytosolic protein Ferritin . this stored iron will be released in a controlled manner depending on demand. It plays the role of a buffer between iron deficiency and iron overload. Ferritin in the serum, functions as carrier for iron. Plasma ferritin is can be used as an indirect marker of the body iron stores. Low levels of hepcidin and iron load can cause organ damage.

Ferritin, a globular protein is made of 24 subunits. When not bound with iron ferritin is known as apoferritin.



STRUCTURE OF FERRITN

In reticuloendotheial cell iron is also stored as hemosiderin. Ferritin is increased in condition of iron over load such as thalassemia , hemochromatosis .

Ferritin being an acute phase reactant and level of ferritin can be falsely high in following condition.

- Inflammation.
- Infection.

The normal range of ferritin is usually between 30–300 ng/mL. Secondary hemochromatosis is a well known complication in thalassemia patients who are on chronic blood transfusion. About 200 mg of iron will be transfused into the body with 250 ml of blood. After about 100 or more transfusions, cardiac dysfunction is documented to occur in thalassemia patient. Serum ferritin increases after 10-12 transfusions in un chelated patients. Estimation of serum ferritin is the traditional way of determining the iron overload[54,55].

B- THALASSEMIA – PATHOPHSIOLOGY:

β- globin chain production is either decreased or completely absent causing an increase in α chains relatively. It leads to low levels of Hb and altered synthesis of globin chains.The sequelae of β thalassemia major is due to two related features. Low levels of normal hemoglobin A secondary to inadequate β globin gene synthesis and unbalanced production of α and β globin chains.

In β thalassemia major, there is absence of β globin chains which causes a relative increase in α chains compared to non – alpha chains. These excess α tetramers are seen as inclusion bodies in erythroid precursors. The α globin

chains are unstable and precipitate in erythroid precursors causing damage to the cell membrane, shortens the life span of erythrocyte leading to anemia. This leads to significantly elevated erythropoiesis with death of red cell precursors in bone marrow.

CLINICAL FEATURES:

THALASSEMIA MAJOR

Homozygous states usally present by 2 months to two years of age with severe pallor, failure to gain weight, growth retardation, cachexia, hepatosplenomegaly. These patients will require chronic blood transfusions and iron chelators[8].

Poorly transfused children have ineffective erythropoiesis features seen as increased metabolic needs, extramedullary hematopoeisis and expansion of marrow spaces[16].

Ineffective erythropiesis causes expanded medullary spaces of facial and skull bones causing frontal and parietal bone bossing, depressed nasal bridge, prominent malar eminence, malocclusion of maxillary teeth giving a chipmunk or thalassemic facies. Deformities of bones are seen secondary to marrow expansion. Un transfused patients can have significant splenomegaly with features of hypersplenism. Abdominal symptoms are also seen.

THALASSEMIA INTERMEDIA:

These patients have a heterozygous state. Clinically have less pallor and remain asymptomatic till about two years of age. They may require blood transfusions.

THALASSEMIA MINOR

These patients have a heterozygous states. Clinically symptoms are minimal, affected children usually have mild anemia which does not respond to iron supplements .HbA2 is more than 3.4%.They can lead a normal life, and do not require regular blood transfusions.

COMPLICATIONS:

Can be due to chronic anemia and tissue hypoxia. Iron overload secondary to increased gut absorption and high levels of erythropoietin. Cardia complications are most common.

CHRONIC ANEMIA: the children present with increasing pallor, decreased activity, failure to thrive, impaired exercise tolerance, abdominal pain, signs of cardiac failure.

CARDIOMYOPATHY IN THALASSEMIA: The most common cause of mortality in transfused patients of TM is heart failure mainly to cardiac iron overload. The pathology in thalassemia is not just the hemolysis and iron overload, but the adaptation of heart to the long standing anemia. Chronic anemia has symptoms like breathlessness and exercise intolerance

which can mask the clinical diagnosis of failure. Cardiac adaptations to chronic anemia can be seen as tachycardia at rest, low blood pressure, increased end diastolic volume, increased ejection fraction and cardiac output that is high.

Cardiac disease in β thalassemia is most commonly seen as a cardiomyopathy which progresses to heart failure and death. It is phenotypically charaterised into-

- **Dialated type :** dilatation of left ventricle and decreased contractility
- **Restrictive type:** left ventricular filling defect, heart failure preceded by pulmonary hypertension

PATHOPHYSIOLOGY: Tt is complex , however the following factors are responsible for cardiac complications[2]

- Chronic hypoxia of tissues secondary to long standing anemia.
- Due to the increased levels of fetal hemoglobin having high oxygen affinity and low levels of 2,3 di phosphoglycerate in donor blood.
- Intrasplenic shunts and liver damage due to extramedullary hematopoeisis increasing the cardiac output.
- Iron overload in heart is thought to be the most common cause of myopathy in thalassemia patients. Free oxygen radicals from Fenton and Haber-Weiss reaction (redox reaction converting ferrous to ferric) are known to cause iron toxicity.

This free iron present in circulation once transferrin is saturated, is labile and through voltage dependant L – type calcium channels enters the cardiac myocyte in ferrous form. This ferrous iron causes apoptosis of cardiac myocytes and ultimately cardiac dysfunction.

- Iron overload increases the susceptibility of myocarditis secondary to viral infections.
- Immunological theory: patients of thalassemia major with heart failure are known to be frequently associated with HLA-DQA1*0501 allele. Whereas patients without heart failure are seen most frequently associated with HLADRB* 1401 allele which is cardioprotective.

PULMONARY HYPERTENSION (PH) IN THALASSEMIA PATIENTS:

- **DEFINITION :** PH is defined as a mean pulmonary artery pressure of 25 mm of Hg or above in an individual at rest at the sea level[31].
- It is a complication seen commonly in thalassemia patients. Reduced nitric oxide availability, endothelial dysfunction, hypercoagubility, increased stiffness of arteries and pulmonary vascular resistance are all implicated in the complex multifactorial etiology of pulmonary hypertension in thalassemia patients[11,14].
- Low hemoglobin levels in TM patients causes a chronic hypoxia[20] condition that can lead to active pulmonary vascular damage. In the hypoxia setting, smooth muscle cells of the pulmonary vasculatur are depolarized by the downregulation of potassium membrane channels.

This causes an increase in intracellular calcium levels which enhances the cellular response to vasoconstrictors. This chain of anemia, hypoxia, vasoconstriction, injury to endothelium, proliferation of smooth muscles and obliteration of pulmonary vasculature reoccur many times in thalassemia patients which ultimately causes pulmonary hypertension.

- Diagnosis of PH in thalassemic patients requires regular and periodic screening as majority of them are asymptomatic, even, a normal systemic blood pressure is seen in patients when the pulmonary pressures are recorded high.
- Frequent blood transfusions cause iron overload in cardia, liver, lung and spleen. Free radical injury due to iron in lungs is also postulated as a possibility for development of pulmonary hypertension by immunoinflammatory pathway. Iron toxicity also causes cirrhosis of liver which can cause PH[21].
- Increased levels of vasoconstrictor endothelin –I, low levels of NO synthase which leads to low level of NO, and high level of arginase (substrate for NO synthesis) secondary to chronic hemolysis and hypoxia in TM lead to pulmonary vasoconstriction.

Various techniques are used to find presymptomatic cardiac complications. They are echocardiography with tissue Doppler Imaging, T2* cardiac MRI, and MUGA scanning.

TRANSFUSIONAL HEMOSIDEROSIS:

Frequent blood transfusions is associated with infections, febrile reactions iron accumulation. One unit of packed red blood cells has 250-300 mg of iron(1mg/ ml). Iron accumulates in chronically transfused children as excretion does not occur .In one transfusion of two units iron accumulated is equal to one year oral intake of iron.

Secondary hemochromatosis in thalassemia is because of inappropriate red cell production, increased hemolysis, defective hemoglobin and increased absorption of iron from gastrointestinal tract. After one year of regular blood transfusions iron starts to accumulate in liver followed by the endocrine glands. It takes about ten years for cardiac decompensation to occur due to iron overload[21].

ENDOCRINE DISTURBANCES:

Iron gets deposited in ferritin form in liver, pancreas, endocrine glands skin heart and other tissues[35,36]. Endocrine disturbances like hypothyroidism, diabetes mellitus, hypoparathyroidism, hypogonadism and hypopituitarism is seen . Short stature can be seen as well[36,37].

OSTEOPOROSIS:

Patients of thalassemia who are dependant on blood transfusions have increased frequency of osteoporosis and osteopenia[38,39]. It can be secondary to endocrine disturbances like hypothyroidism and hypoparathyroidism also.

Desferrioxamine chronic ingestion causes disc disease. It is usually seen in second decade[40].

These children present with fractures, low back ache , short stature, bony deformities.

INFECTIONS:

Complications associated with blood transfusions is infections like, HIV, CMV, hepatitis B and hepatitis C. Opportunistic infections are seen due to iron overload. Yersinis entercolitica grows well with excessive iron .Clinical features are fever and diarrhea[41]. It can be treated with cotrimaxazole and aminoglycosides. Infections caused by Listeria monocytogenes and Rhizopus oryzae is also seen commonly in thalassemia patients. Following spleenectomy these children are highly susceptible for developing infections by capsular micro organisms.

Other complications are gall stones, hepatocellular carcinoma, gout secondary to hyperuricemia[42].

PSYCHO/SOCIAL FACTOR

Repeated and frequent transfusions tamper the quality of life. Chronic illness impairs the psycho social stability and leads to poor complaince. Due to these factors, thalaseemia has a negative impact on HRQOL(Health Related Quality of Life)[43].

Children with multiple transfusions have increased prevalence of problems related to behaviour. Hemosiderotic patients are known to have impaired abstract, remain attention deficit, have poor memory, defect of language, constructional, visual spatial skills[44,45,46].

INVESTIGATIONS:

1. Complete blood count: Hemoglobin is normal to severely reduced. MCV, MCH, MCHC will be reduced.
2. Peripheral blood smear: Shows marked microcytic hypochromic anemia, anisopiokiocytosis, polycytosis, nucleated cells, target cells, pencil cells, basophilic stippling, rarely immature WBCs.
3. Red cell distribution width (RDW) is increased indicating anisocytosis.
4. Reticulocyte count: Reticulocytosis is seen as marker of increased erythopoiesis due to increased hemolysis. Corrected reticulocyte count more than 2.5 % is taken as evidence of increased bone marrow activity. Due to ineffective erythopoiesis in the bone marrow it will be less than 8%.
5. Mentzers Index: Mentzer index helpful in differentiating iron deficiency anemia from beta thalassemia. The index is calculated from the quotient of the mean corpuscular volume (MCV) divided by the red blood cell count (RBC). If the value is less than 13 thalassemia is probable diagnosis and if its more than 13 it indicates towards iron deficiency anaemia[27].

6. An elevated LDH and unconjugated bilirubin is usually seen indicating ineffective erythopoiesis. Serum iron and ferritin is elevated.
7. X-ray showing widening of medulla due to bone marrow hyperplasia thinning of cortex and long bones show trabeculation, including the metacarpals and meta tarsals.
8. Hemoglobin electrophoresis: Using this test we can classify into thalassemia major, intermedia and minor based on the level of HbA, HbF & Hb A_2.
9. Ultrasound abdomen : for confirmation of hepatosplenomegaly.
10. Genetic analysis : It helps to know the type of mutation and classification of thalassemia.

ECHOCARDIOGRAPHY:

Echocardiography is the most commonly used non invasive technique for systolic and diastolic functions, ventricular size assessment, and evaluation for pulmonary arterial hypertension. Pericarditis and valvular involvement can also be picked up.

These parameters are included in echocardiography 2D and M-mode: It is used primarily for measurement of ventricular dimensions like wall thickness and size, systolic functions ,fractional shortening and motion abnormalities of cardiac valves.

Doppler Echocardiography: it is a combination study of blood flow profiles with the cardiac pictures. Two methods commonly done are pulsed wave and continuous wave. The velocity of tricuspid and pulmonary regurgitant jets and its severity can be assessed by this technique[29].

MAGNETIC RESONANCE IMAGING:

It is the gold standard for evaluation of cardiac iron load. It provides a quantitive ventricular function, tissue characterization, viability of the myocardium. Cardiac MRI assessment of T2* and ejection fraction on yearly basis is best in a good set up. Cardiac T2* is useful for cardiac iron load assessment, it is the time taken for decay of myocardial signal by 63% and is measured im ms(milliseconds). Based on it risk of cardiac iron load is divided into low , intermediate and severe when it is >20ms,10-20ms,and <10ms respectively.It can assess the preclinical cardiac dysfunction.

It does not have operator variability, however cost and non availabilty in resource poor setting are disadvantages for wide use[29].

TRANSFUSION THERAPY [47,48,49]

Blood transfusion is indicated when

i. Hb < 7gm/dl
ii. Features s/o extramedullary erythropoiesis like facial changes
iii. Inadequate growth & fractures

Prior to transfusion, children should be evaluated

Anemia, growth & development, skeletal changes, organomegaly (liver & spleen), facial changes,

Laboratory work up[48].

Complete blood count, red blood cell indices, peripheral smear, liver function tests, molecular diagnostics, hepatitis serology, HIV screening, blood grouping & cross matching, dentition.

Pre transfusion hemoglobin should be maintained between 9.5 to 10gm/dl. Once in 2 to 5 weeks (moderate transfusion). Number of transfusion should be less than 200ml/kg) year. Super transfusion and hypertransfusion regimes maintaining pre transfusion Hb of more than 12gm 1dl and 10gm 1d1 is not regularly practiced. Safe transfusion techniques should be followed.

CHELATION THERAPY:

The main motive of chelation therapy is to prevent tissue damage caused by transfusional hemosiderosis and iron overload because of thalassemia per say. i.e to increase the excretion of iron and prevent accumulation and toxicity.

Indications for initiation of chelation therapy are[8]:

- Blood transfusion of one year corresponds to iron overload
- serum ferritin of 1000ng/ml
- more than 2500 micro gram dry weight of liver iron concentration.

Currently three iron chelators are available:

- Desferrioxamine ,deferasirox, deferiprone

DESFERRIOXAMINE:

It can be administered both subcutaneously as well by intravenous route.

Dose : 20 – 50 mg / kg per day, given for five to seven days a week.

Half life- < 30 minutes.

Subcutaneous infusion has to be given slowly over 8 to 12 hours as a 10 percent solution. Local skin reactions can be minimized by applying a local anesthetic prior to starting infusion and following the recommended strength and duration of infusion.

Systemic side effects like high frequency hearing loss, cataracts, night blindness due to retinal damage, disproportionate truncal growth causing short stature are seen.

Patients should be monitored once in a year for these side effects.

Major draw back is poor compliance because of route of administration and side effects. Hence the newly available oral iron chelator is preferred.

DEFERIPRONE:

Its an oral iron chelating agent, available in India.

One atom of iron is bound by three molecules of deferiprone and excreted in urine.

Dose : 25mg/kg three times a day.

Half life: 3 hours.

Very useful in decreasing cardiac toxicity due to iron.

Side effects: agranulocytosis, neutropenia, arthropathy, gastrointestinal symptoms, zinc deficiency. Hence monitoring of weekly white blood cell count should be done as death is reported rarely.

DEFERASIROX:

Two molecules of this combine with one molecule of ferric iron to form a complex.

Dose: 20-30mg/kg once a day orally in empty stomach.

Half life -16 hours.

Side effects: renal dysfunction , gastrointestinal disturbances, skin rashes elevated transaminases.

HYDROXYUREA:

This drug is used to increase the level of HbF which indirectly decreases the hemolysis.

STEM CELL TRANSPLANTATION:

It is the definitive cure therapy for thalassemia patients. The option for stem cell transplant should be given to all patients who have a HLA matched sibling[8,16].

GENE THERAPY: Is under trail and hope fully it will be available in future[8,16].

PREVENTION OF COMPLICATIONS

- By adequate regular transfusion to maintain adequate growth and prevent extramedullary erythopoeisis.
- Iron chelation theraphy – to prevent end organ damage like liver, cardiac failure and endocrine disturbances.
- .Prevention of infections transmitted by blood transfusion by effective screening promoting the quality of voluntary blood donators, leucodepleted packed red blood cells.
- Treatment of cardiac complications is mainly by iron chelators. More than half the patients with failure are known to improve with parenteral desferrioxamine infusion and a combination therapy with deferiprone[37], diuretics. Ionotropes and anticoagulants are also used.
- Trials are on for treatment with sildenafil, inhaled nitric oxide, bosenatan and arginine for treatment of pulmonary hypertension in thalassemia patients. Eporostenol an antithrombotic agent has also been reported to be useful in treatment of PH in thalassemics

PREVENTION OF COMPLICATIONS by monitoring:

Regular follow up of patients and monitoring complications related to blood transfusions, iron overload, other supportive measures like growth monitoring, assessment of liver functions and kidney functions by blood tests, endocrine complication like diabetes , short stature , hypothyroidism, hypoparathyroidism should be seen. Ophthalmological and auditory evaluation for chelation toxicity should be done in children of more than ten years of age.

PREVENTION

Pre natal diagnosis is essential for prevention as the prevalence of carriers for thalaseemia is 3 to 11 % in India[47].

Sardinia[5] and Cyprus have programmes for increasing thalassemia awareness resulting in more number of people undergoing screening tests. Genetic counselling and prenatal testing in these countries showed a decline in thalassemia from 1 in 250 to 1 in 4000 births.

Medical termination of pregnancy for thalassemia is permitted in Iran if conception is less than 16 weeks.

Prenatal diagnosis can be done by the following methods[34]

- Chorionic villous sampling(CVS)
- Amniocentesis
- Per cutaneous umbilical blood sampling(PUBS).

Chorionic villous sampling:

It is performed at 10-12 weeks of pregnancy where adequate DNA is obtained by ultrasound guidance. Placental tissue sample is taken by a catheter that is placed trans cervically or trans abdominally and trophoblast cells are analysed.. Genetically abnormal fetus can be picked up at the earliest by CVS. Pregnancy loss rate is 0.5 to 1 percent when performed by skill full hands. Complications of performing CVS earlier are limb reduction defects of fetus and other abnormalities in oro mandibular development[34,47].

Amniocentesis :

Amniotic fluid containing fetal cells is taken in second trimester through ultrasound guided images. Around 20 ml of amniotic fluid is removed for analysis which will be replaced by fetus in a day. α and β thalassemias can be detected by direct detection of a DNA mutation. Mutation is accomplished by allele specific oligonucleotide analysis. In α thalassemias, deletion of DNA can be seen as change in the DNA fragment size after a PCR. Incidence of fetal loss is 0.5 to 1 percent. Limb anomalies can also be seen[34,47].

Percutaneous umbilical blood sampling: (PUBS)

It is a procedure performed from second trimester till term with ultrasound guidance. It not only provides access for in utero treatment but also diagnostic samples for hematological, cytogenetic, DNA and immunologis

studies is obtained. Risk of fetal loss: 1 to 2 percent. Complications- 5 percent chances of preterm delivery.

Cordocentesis:

About 2 to 3 ml of fetal blood is aspirated and analysed for globin chains by gel electrophoresis. An α/γ synthesis ratio more than 0.02 to 0.03 suggests a normal fetus. Its is rarely practised .

As prenatal testing is costly and an emotional burden to parents i. e losing a pregnancy if thalassemia is detected, it is better that pre marital testing and genetic and screening tests be done at school level.

REVIEW OF LITERATURE.

A descriptive observational study was done by Samira Z Sazed etal, on 56 patients of beta thalassemia major attending hematology opd at children university hospital, Al Minia University . Study duration was from February 2009 to april 2011 at Egypt to detect early cardiac involvement in beta thalassemia patients.

56 of thalassemia major patients who received blood transfusions ≥ 12 a year were part of research. Patients were divided based on the iron overload diagnosed by the serum ferritin values into three groups[12].

1. serum ferritin < 2500ng/ml- 21 patients.
2. Serum ferritin 2500 -5000ng/ml -23 patients.
3. serum ferritin > 5000 ng/ml 12 patients.

These patients were evaluated clinically and investigated with serum ferritin, ecg and echocardiography. Corrected QT intervals and QT dispersion was seen in ecg. Systolic and diastolic functions of left atrium was assessed by echocardiography and tissue Doppler imaging. Results was groups 2 and 3 with serum ferritn values of more than 2500ng/ml and more than 5000ng/ml respectively had a significant increase in left ventricular septal and posterior wall thickness compared to group 1 with serum ferritin values less than 2500ng/ml.

QTc and QTd was increased significantly in group with serum ferritin more than 5000ng/ml compared to the group with serum ferritin less than 2500ng/ml.

Groups 2 and 3 had significantly impaired emptying fraction and LV diastolic function compared to 1.Tissue Doppler imaging showed impaired LV systolic function in group 3 than group 1 with significant difference by standard echocardiography. Conclusion was increase in left ventricle septal and posterioir wall thickening was seen earliar to changes in ecg, left ventricular diastolic dysfunction and impairment of left atrium active emptying fraction is seen earlier than left ventricular diastolic dysfunction.

Another study done by Noor Mohammad Noori etal at Iran for early diagnosis of cardiac dysfunction by a comparison of QT dispersion with left ventricular mass index in thalassemia major patients[24].

1. To compare the diagnostic value of corrected QT dispersion and QT dispersion with the left ventricular mass and left ventricular mass index.
2. To determine the specificity and sensitivity of these in early detection of involvement of cardia in thalassemia major patients.

It was a case controlled study done on 60 patients of thalassemia major patients older than 10 years of age and compared with healthy subjects who matched with sex and age. They observed that cases had a mean age of 16.08+_ 2.8 years and controls had a mean age of 16.08+_3.01 years respectively.male :

female ratio was 33:27 in cases and 31:29 in controls.Case group had a greater mass index than the control group.

Case group had a larger QTcd and QTd than the control group.

The sensitivity and specificity was as follows

	Sensitivity	**Specificity**
LV mass	88.3%	77.1%
LV mass index	86.7%	80%
QTcd	93.8%	80%
QTd	91.7%	86.7%

They concluded in the study that sensitivity and specificity of QTcd ,QTd compared to LVmass was acceptable. In asymptomatic patients of thalassemia major standard ecg can be used as for early diagnosis of cardiac involvement[24].

A prospective study by Ameen Mosa etal done at department of cardiology[23], Duhok University, Iraq on beta thalassemia intermedia patients showing the cardiac complications .It was done to correlate the clinical features of cardiac complications of thalassemia intermedia patients with echocardiograph. The standard echo of 2D, M mode was performed on 31 females and 30 males to know the cardiac chamber dimensions. Tricuspid regurgitation velocity was recorded using continuous Doppler. Diastolic function of left ventricle was evaluated using pulsed Doppler of inflow of mitral valve. Patients were divided into three groups based on the tricuspid

regurgitant velocity to correlate echocardiographic and clinical findings. Mean age of patients was 19.6 years. They observed that the first group- tricuspid regurgitant velocity <2.5 m/sec was seen in 42 patients(69%).Second group with tricuspid regurgitant velocity 2.5 to 2.9 m/sec was seen in 11 patients(18 %).Third group with tricuspid regurgitant velocity > 3 m/ sec was seen in 8 patients (13 %). Congestive cardiac failure was seen in 3 patients(4.9%).Group three patients were older and had more males with low hemoglobin and high ferritn values. Age at diagnosis and first blood transfusion was at a later age. Clinically they were symptomatic and had exertional dyspnea. Echocardiagraphy revealed increased right ventricular diameter and size of right atrium. They also had low ejection fraction relatively.

Tricuspid regurgitant velocity was associated positively with age, pulmonary regurgitation and cardiac volumes when used as a continous predictor. Negative association was seen with ejection fraction.

The conclusion was that echocardiography is a useful test for early evaluation of cardiac condition. It can reveal many abnormalities of cardiac complications in thalassemia intermedia patients.

Thalassemia intermedia patients should be necessarily offered echocardiographic assessment early in life.In thalassemia intermedia patients echo derived complications of left and right side of heart are not uncommon. In this which was extended , it was further concluded that inTI, PH is the leading cause of heart failure[23].

A study of echocardiographic parameters of left ventricle systolic and diastolic function in patients with β thala ssemia major was done by Asaad Abdullah Abbas etal at Ibn Albalady Hospital for Children and Maternity at Baghdad[22]. It was cross sectional descriptive study was done on a total of 427 thalassemia major patients receiving regular blood transfusions and chelation.

Objective was to assesss the left ventricular systolic and diastolic parameters in β- thalasemia major children and its relation to spleen status and ferritin level. It was a cross sectional descriptive study done on thalassemia major patients who were on regular blood transfusions and chelation. A gap of minimum of 48 hours was there between blood transfusions and analysis of cardia by echocardiography. procedure was done as per the guidelines of American Society of Echocardiography for paediatric patients. M –mode, 2D and Doppler echocardiography was averaged to 3 cardiac cycles

The results wre that

- Left atrium , aortic diameter , left ventricular posterior wall thickness, LA/AO ratio, interventricular thickness , LVEDd,LVEDs diameter was increased in thalassemia major patients.
- thalassemic patients had higher stroke volume, MPI and L V mas index . fraction shortening and ejection fraction showed no changes.
- thalasemia patients also had higher peak A, peak E and isovolumic relaxation time. But E deceleration time and E/A flow ratio showed no difference in comparison with the controls.

- i-mitral valve parameters by Doppler showe no effect in relation to serum ferritin level and spleen status.

They concluded that patients of beta thalassemia have a systolic function that is good but diastolic function is decreased. There was no relation between the systolic and diastolic functions of LV and serum ferritn levels.

In an observational study done done by Meloni A etal, 60 thalassemia major patients were included in the study. They reported the echocardiography findings in these patients[11]

Echo was done to evaluate the association between tricuspid regurgitant velocities , serum ferritin , dyregulation of arginine and serological markers of hemolysis. They observed that low risk of pulmonary hypertension was found in well transfused thalassemia major patients than thalassemia intermadia patients. Vascular stressors was found in thalassemia major patients that increased the life time risk of pulmonary hypertension to levels that is higher than that of the general population.

Their study supported the recommendations of yearly screening of thalassemia major patients by echocardiography.

They conclude that patients with persistent TRV of more than 3m/s need cardiac catheterization.

A study done by A. Azarkeivan etal, published in Medwell journals, 2009,showed the involvement of cardia in transfusion dependant β thlassemia

major patients. It was done to study cardiac complications in transfusion dependant beta thalassemia patients[56].

It was a descriptive study done at Ali Asghar Childrens Hospital an Adult Thalassemia Clinic. Study sample-139 patients more than 7 years of age on regular blood transfusions and chelation therapy. History regarding duration of blood transfusion, age sex, respiratory complaints, signs of failure was asked. Physiscal examination was done.

These patients were subjected to chest xray, Ecg, arterial blood gas analysis, and echocardiography.following observations was made.

1. thalassemia major patients-104, thlassemia intermedia patients-35.

Age	21.2±7.1years
Serum ferritin	15,362±1609 ng/dl
Ejection fraction	60.3± 9.7 %
LVEDV	4.70±.6 mm3.
Desferioxamine	52.1±.10.9 mg/kg

2. No correlation found between LVEDV and age and significant correlation was found between LVEDV and ejection fraction.

They concluded that significant correlation was found between age of transfusion dependant thalassemia patients and cardiac failure. Well chelated patients can have alteration in cardiac functions. Regular follow up echocardiography is essential in thalassemia patients. Serum ferritin is not ideal for assessment of body iron store.

An study published by Sara Malik , on complications seen in beta thalassemia patients who are transfusion dependant shows that more 50 % of mortality in these patients is secondary to cardiac disorders[1].

Heart complications can manifest as cardiac failure, rhythm disturbances, hemosiderotic cardiomyopathy, pulmonaty hypertension, pericarditis, myocarditis. Reasons for cardiac decompensation are- iron overload, immunologic factors (major histocompatibility antigens), genetic,

chronic anaemia, infections.

Endocrine complications like short stature , delayed puberty , gonadal dysfunction are also seen in these patients. Reasons implicated for dysfunction of multiple endocrine organs are:

- chronic anemia
- deficient micronutrients
- low levels of IGF -1; IGFBP-3
- deposition of iron in pancreas

Metabolic complications: low levels of trace elements is seen

Hepatic complications: manifests as hepatomegaly, increased liver enzymes, fibrosis.

Hepatocellular carcinoma can complicate co existing infections of hepatitis B and C.

Other complications like low IQ, infections, hypersplenism is also seen in chronically transfused patients.

Conclusion was that prevention by antenatal testing , premarital screening and genetic counseling should be done. And stem cell transplantion is the definitive cure.

In a study by Noor mohammad Noori etal, diagnostic value of Ecg in measuring the left ventricular mass index was compared with echocardiography. Study was performed on thalassemia major patients at a children hospital in Iran who were more than ten years of age[24].

82 patients of which 40 were women and 42 men were asymptomatic at the time of investigation. They finally concluded that echocardiography was more accurate in knowing the left ventricular mass index than electrocardiography.they also noted an increase in the LV mass and there was no correlation between QT changes in ecg and LV mass in echocardiography.

K, Papadopoulou et al in their study done on 93 beta thlassemia major patients in the age group of 2.5 to 18 years found that the patients with good compliance to chelation therapy had lower incidence of overt heart disease compared to poor compliance patients. they also found that left ventricular end diastolic dimension , left ventricular mass and LV mass index was increased compared to normal controls of same age and gender and that these were the earlier signs of dilated cardiomyopathy on echocardiography[26].

Cardiothoracic ratio was increased in 8 % and ecg abnormalities seen in 12 5 of the patients, and only 9 % of them had abnormalities detected in echocardiography.

In a study by Tanner etal it was found that combined chelation with oral deferiprone and subcutaneous deferoxamine improves myocardial function by decreasing cardiac iron load. They also observed that LV ejection improved along with myocardial function following combined chelation therapy[31].

In a study by Sylvia etal at Childrens Hospital Oakland Research Institute , California, 25 patients of thalassemia (TM=18, TI=7), aged 10 years and above, 17 of them were found to have PH, of which 56%(n=10) of them were TM and 44%(n=7) were TI patients respectively. However all the TI patients had PH[28].

Mean hemoglobin level was 9.5 gm/dl, lower than the patients without PH. Mean serum ferritin was higher than the patients who did not have PH. Mean age was higher than those without PH.

They concluded that mild to moderate pulmonary hypertension had high prevalence in well transfused TM and most importantly in TI patients.

And platelet activation might have a role in development of PH in these patients.

AIM OF THE STUDY

1. To study the cardiovascular complications in beta thalassemia major / intermedia patients aged 2 to 12 years on regular blood transfusions and
2. To establish the significance of echocardiography in these patients.
3. To study the clinical profile of beta thalassemia major/ intermedia patients coming to Institute of Child Health and Children Hospital, Chennai.

OBJECTIVE

- To evaluate β thalassemia patients of 2 to 12 years of age using echocardiography
- To study the co relation between serum ferritin level and cardiac function through echocardiography in these patients.
- To compare echocardiography findings in β thalassemia major and intermedia patients
- To study the clinical profile of thalassemia major/ intermedia patients attending tertiary care centre at Institute of Child Health and Children, Chennai.

STUDY JUSTIFICATION

1. Hemoglobin disorders are the cause for about 3.4% death in children younger than 5 years.
2. Despite advances in therapeutic management of thalassemia resulting in remarkable improvement in survival of patient, heart disease remains the most common cause of moratlity and morbidity.
3. Congestive cardiac failure and arrthymias are potentially lethal complications of increased iron load in thalassemia patients.
4. In India, studies regarding regular screening of cardiac complications in first decade by echocardiography are minimal.
5. Though cardiac MRI is gold standard in evaluating cardiac iron load, due to the disadvantages, (cost, time consuming, non availability in resource poor setting, claustrophobia, contraindications in patients on cardiac pace maker and metallic fragments and bodies). Echocardiography is widely used.
6. Advantages of Echocardiography are it is cost effective, widely available, less time consuming, does not require anaesthesia, can be used as non invasive screening test in thalassemia patient.

METHODOLOGY

Design of the study: Hospital based cross sectional study.

Place: Institute of child health and children hospital.

SAMPLE SPECIFICATIONS:

Case definition: Cases of thalassemia major / intermedia confirmed clinically and by hemoglobin electrophoresis on regular blood transfusions.

Inclusion criteria:

1. Thalassemia major /intermedia patients in the age group of 2 to 12 years.
2. Who are receiving regular one or more blood transfusions per month for two or more years.
3. Diagnosis confirmed as thalassemia major/ intermedia clinically or by hemoglobin electrophoresis.

Exclusion criteria:

1. Thalassemia patients with known cardiovascular complications or congenital heart diseases.
2. Patients with terminal illness.
3. Patients or parents not giving consent to participate in the study.

Sample size: 54

CONFLICT OF INTEREST: nil

FINANCIAL SUPPORT: nil

Ethical Committee clearance was obtained from the institutional review board.

MATERIALS AND METHODS

SUBJECT SELECTION:

Patients of thalassemia major and intermedia in the study age group on regular blood transfusion and chelation therapy attending tertiary care centre satisfying the inclusion and exclusion criteria were recruited into the study after getting informed parental consent.

History and analysis of old records was done for the following-

- Age at diagnosis
- Consanguinity
- Frequency of blood transfusions
- Number of transfusions
- Hemoglobin electrophoresis report- thalassemia major/ intermedia
- Family history to know the number of affected/ normal/ carrier siblings

- Duration of chelation therapy
- History suggestive of cardiac illness such as easy fatiguability, palpitations,hurried breathing
- Whether patient is a known case of cardiac disease or not

ANTHROPOMETRY:

It included measurement of height , weight and body surface area of the subjects and plotted on standard charts and assigned Z scores.

VITALS:

Heart rate, respiratory rate and temperature was measured. Both systolic and diastolic blood pressure was measured.

Signs of pallor, jaundice was seen.

Systemic examination was done.

Cardiovascular system-for evidence of murmurs, rhythm disturbances.

Respiratory system-to rule infections of lung parenchyma.

Abdomen for evidence of hepatomegaly and splenomegaly.

INVESTIGATIONS:

Complete blood count: for hemoglobin, total wbc count. Platelets estimated using autoanalysers.

Chest xray was done to look for of evidence of cardiomegaly

Serum ferritin to know the iron load, using chemiluminescence technology.

Ecg to know rhytm disturbances and Qtc interval

Echocardiography: the following parameters was assessed -LVIDd, LVIDs, IVS thickness , posterior wall thickness to know LV mass. To evaluate cardiac function ejection fraction, fraction shortening, by trans thoracic 2D, M mode echocardiography. TR velocity and pulmonary pressure gradient for estimation of pulmonary hypertension by continuous wave Doppler.

MATERIALS:

Details of the patient – present age, sex, age at diagnosis.

Type of thalassemia (major / intermedia)- clinical severity varies with the type of β- thalassemia. Patients of beta thalassemia major require frequent transfusions at 2 to 6 week intervals but those of thalasemia intermedia need less frequent transfusions. However patients who are transfusion dependant were included in the present study.

Residence: to know the prevalence of the disease and geographical distribution

Family history: To know consanguinity, sibling history (to know the number of affected/ deaths/ carriers/ normal children)

Duration of the disease and frequency of blood transfusions: to know the chronicity of disease and to estimate the severity of iron overload with transfusions, cardiac dysfunction, growth.

Chelation therapy: whether patient was on oral chelation therapy/ not

If yes, then the duration and dose of oral chelation therapy. In our hospital patients received deferasirox tablets (dose 10 -30mg/ kg /day once a day in empty stomach)

ANTHROPOMETRY:

Height for age: Standing height of the child is measured using stadiometer where occiput, shoulders, buttocks , heels are touching against the vertical board. Head is positioned in Frankfurt plane. Height for age is plotted in the standard growth chart (WHO growth chart 2015).

Weight for age: It is obtained by measuring weight in kilograms and plotted using WHO chart.

Body surface area: weight in kilogram and height in cm plotted on body surface area nomogram

Features of anemia like pallor, is seen .

Vitals :

Heart rate –tabulated as normal or tachycardia based on PALS(Paediatric Advanced Life Support)

Age : 2 years to 10 years- normal(60-140), > 10 years -60-100per minute. Tachycardia is more than the upper limit of normal for age.

Respiratory rate-rate more than the upper limit of normal for the corresponding age was considered as tachypnoea.

1 year to 3 years :24-40 per minute

4 years to 5 years :22 to 34per minute

6 years to 12 years:18 to 30 per minute.

Temperature:measured in axilla: normal is 36.5°C to 37.5 $^{\circ}$C.

BLOOD PRESSURE: is measured using sphygmomanometer with age appropriate size cuff, patient in sitting position. An average of three readings of systolic and diastolic BP is plotted on NHBPEP (National High Blood Pressure Education Program , 2004) normogram.

Blood pressure more than 95th percentile for age and gender is considered as hypertension.

Complete blood count: to know the hemoglobin and indices prior to transfusion and echocardiography.

Serum ferritin: sample for serum ferritin was collected during cannulation prior to blood transfusion .

Hemoglobin electrophoresis: report was used to classify thalassemia into major and intermedia

Chest X ray: was done to look for evidence for cardiomegaly using cardiothoracic ratio for age

Electrocardiogram: Standard 12 lead ECG was done at admission. Based on R/S ratio RVH is present when R/S ratio is increased and LVH when R/S ratio is decreased in these leads QT_c interval was calculated using standard formula. Bazzet's formula=$QT/\sqrt{RR interval}$. According to this normal QTc interval is 0.44 seconds in children 6 months and older. This can be increased in myocarditis and dilated and hypertrophic cardiomyopathies.

Echocardiography: Echocardiography was performed on patients using a Philips Envisor ultrasound machine having a transducer of 3.5/5 and 2.5/5 MHz. 2 D, M mode, and Doppler echocardiography was done as per the guidelines of American society of echocardiography. LV end diastolic diameter, LV end systolic diameter , systolic and diastolic interventricular septum diameter, LV posterior wall thickness in systole and diastole was calculated using M – mode echocardiography. Ejection fraction and fractional shortening was also calculated using the same.

L V mass was calculated using the formula 0.8×1.04× ((LV end diastolic diameter+ Posterior wall thickness+ interventricular septum thickness)$^{3-}$ (LV end diastolic diameter)^3)+0.6. and LV mass index was indexed to body surface area. Tricuspid regurgitant velocity was measured by pulsed Doppler.

Pulmonary hypertension was measured using tricuspid regurgitant jet velocity and modified Bernoulli equation ($\Delta P=4V^{2)}$. Pulmonary hypertension was diagnosed when the mean pulmonary artery pressure is >25 mm of Hg.Echocardiography was done on 54 patients in the age group of 2 to 12 years atleast 48 hours after the last transfusion, in a supine position .

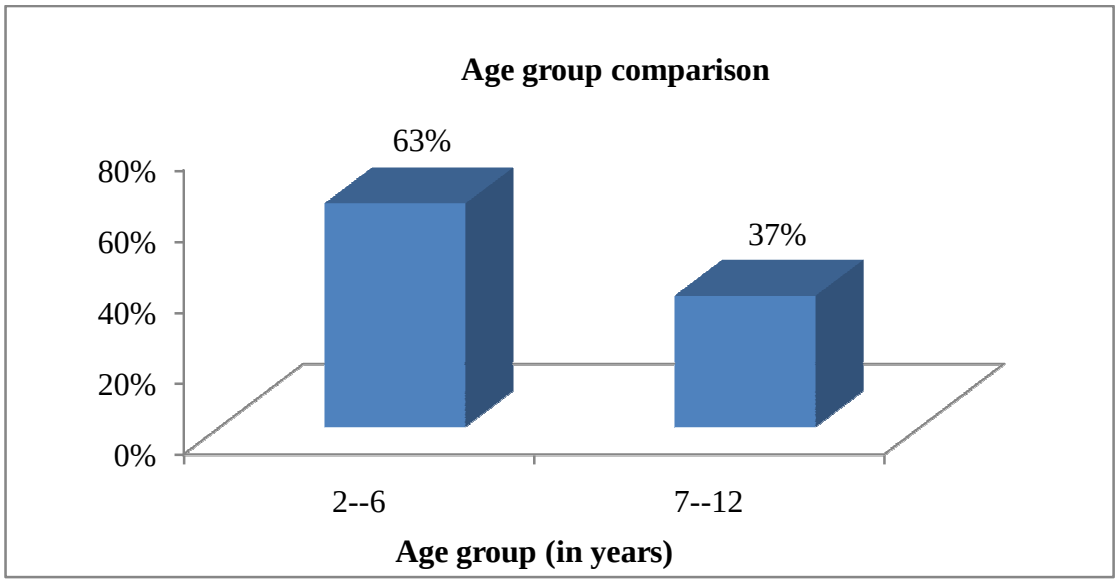
STATISTICAL METHODS

The history of patient, anthropometry, physical examination findings, laboratory investigations , echocardiography findings were collected from the children included in the study and recorded in data collection form. The data entered in excel sheet. Data analysis was done by using epidemiological information package in computer. Frequencies, means , percentage , standard deviations, fisher's exact test, co-efficient of correction values and p value were calculated by using SPSS software frequencies.

OBSERVATION AND RESULTS

Age wise distribution of cases

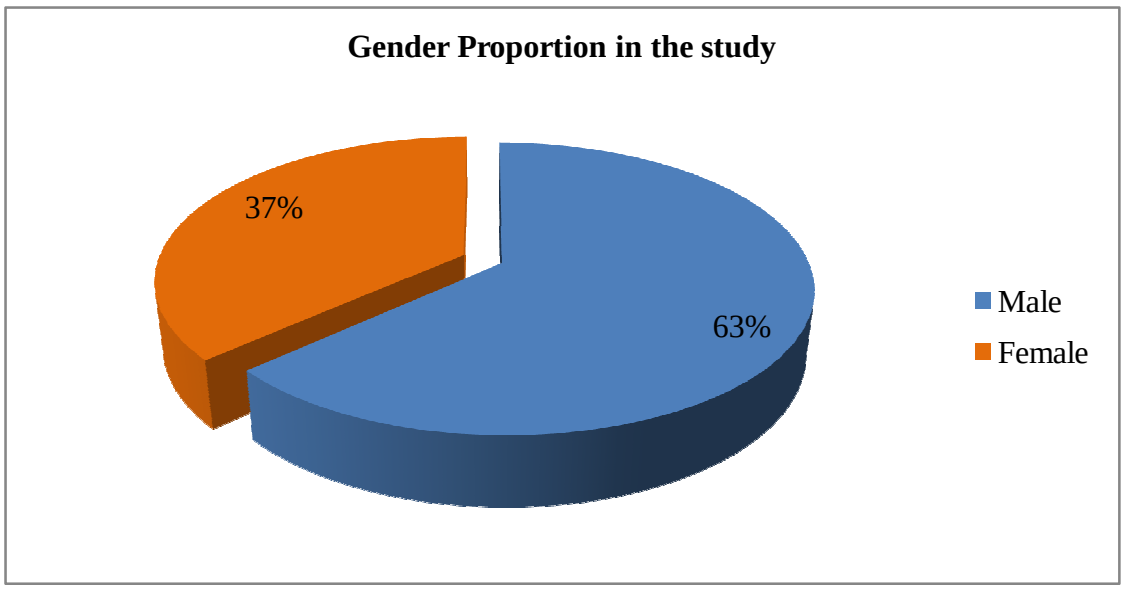
Age (in years)	No. of patients	%
2—6	34	63%
7--12	20	37%
Total	54	100%



In the present study, there were 63% (n=34) in the age group 2 to 6 years and 37% (n=20) were of age group 6 to 12 years.

Gender distribution of cases

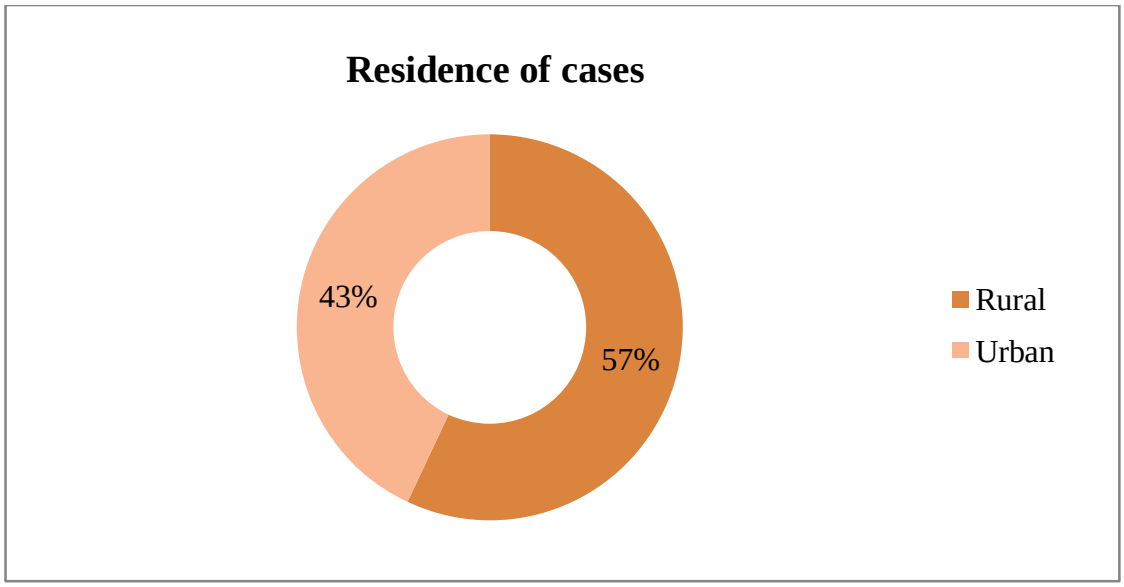
	No. of patients	%
Male	34	63
Female	20	37



In the present study, male patient were predominant with 63% (n=33) as compared to female patient 37% (n=20).

Geographical distributions of cases

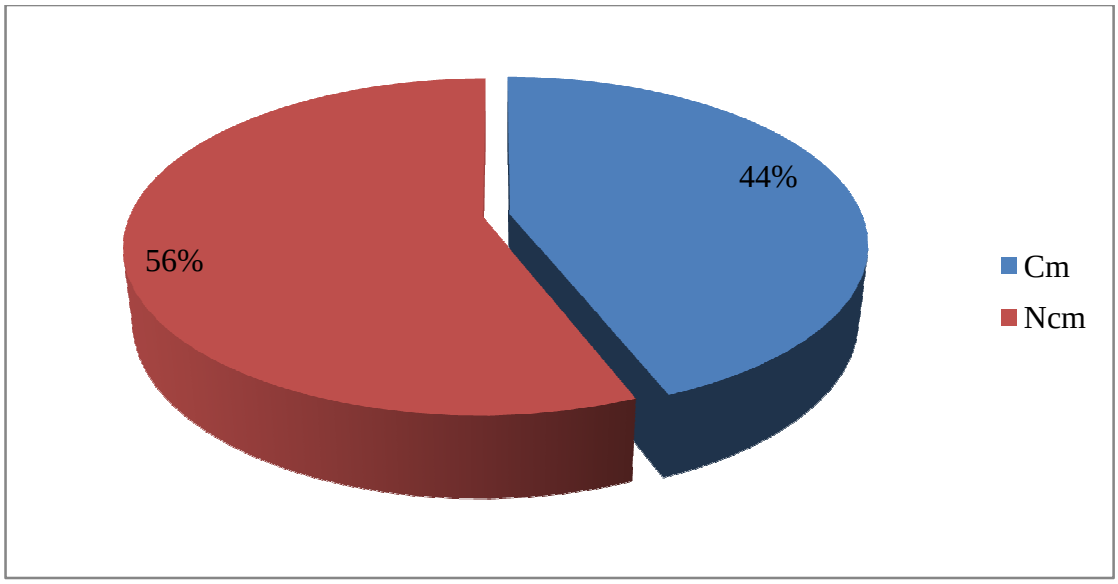
AREA	No. of patients	%
Rural	31	57
Urban	23	43
Total	54	100



In this study, children belonging to rural area accounted for 57% (n=31) which is predominant as compared to children from urban area 43% (n=23)

Type of Marriage

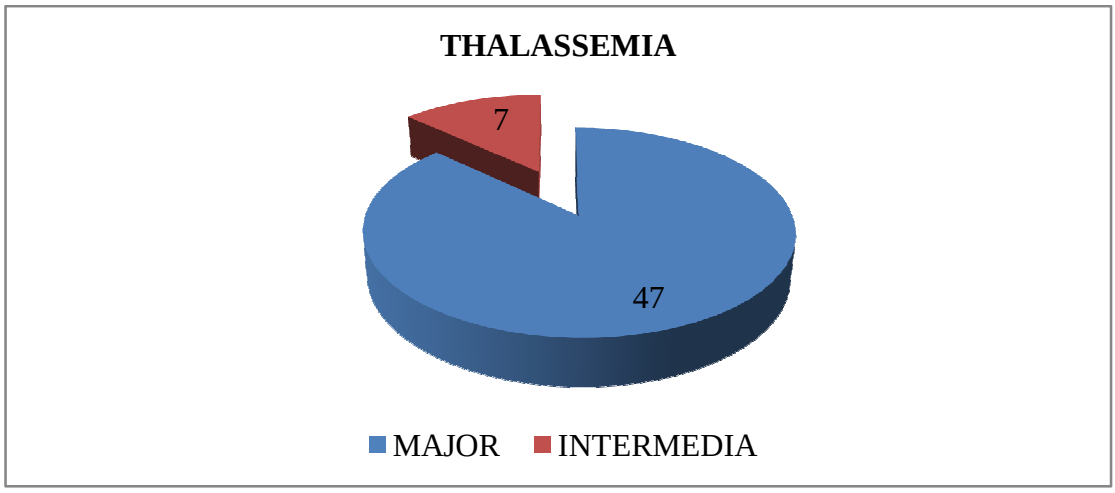
Type of marriage	No. of patients	Percent
Consanguineous	24	44 %
Non consanguineous	30	56 %
Total	54	100 %



In the this study, 56% (n=30) were children born to parents with non consanguineous marriage and 44% (n=24) were born to consanguineous married couple

THALASSEMIA

Hb electrophoresis	No. of patients	Percentage
Intermediate	7	13%
Major	47	87%
Total	54	100%



In this study, 87%(n=47) were patients with thalassemia major and 13%(n=7) were patients of thalassemia intermedia.

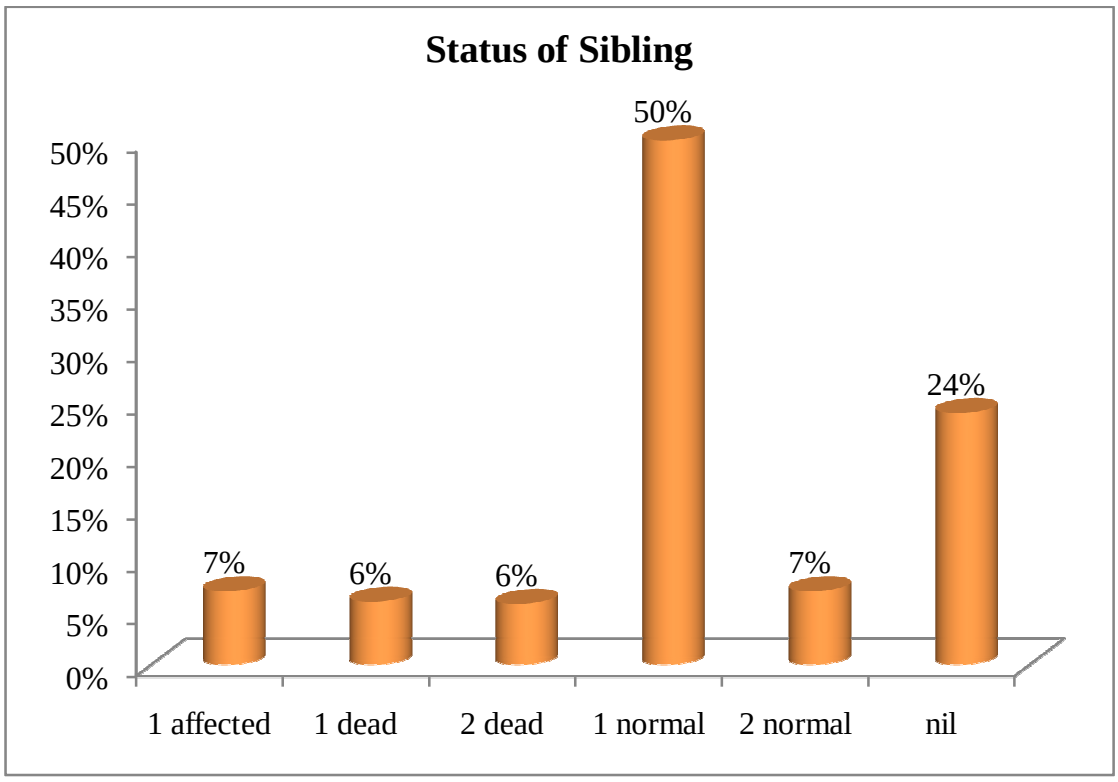
Frequency of transfusion

Transfusion	n	Percent
Monthly	47	87%
2 months	5	9%
3 months	2	3%
Total	54	100 %

In our study, 85 % (n=46) received transfusion monthly, while 9% (n=5) received blood transfusion once in 2 months and 6% (n=3) received transfusion once in three months

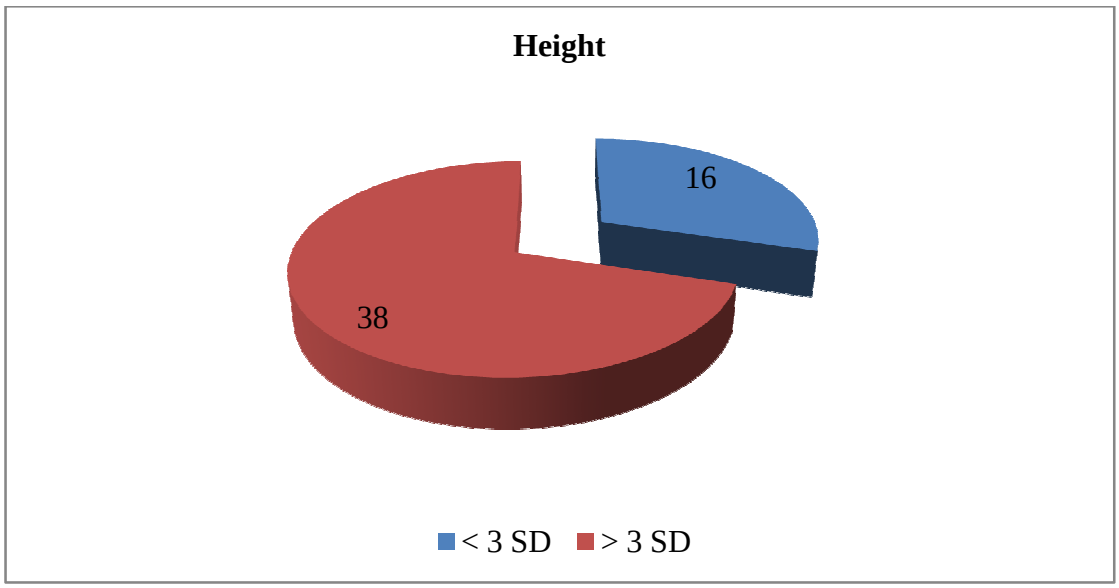
Family history

Sibling	n	Percentage
1 affected	4	7%
1 dead	3	6%
2 dead	3	6%
1 normal	27	50%
2 normal	4	7%
Nil	13	24%
Total	54	100%



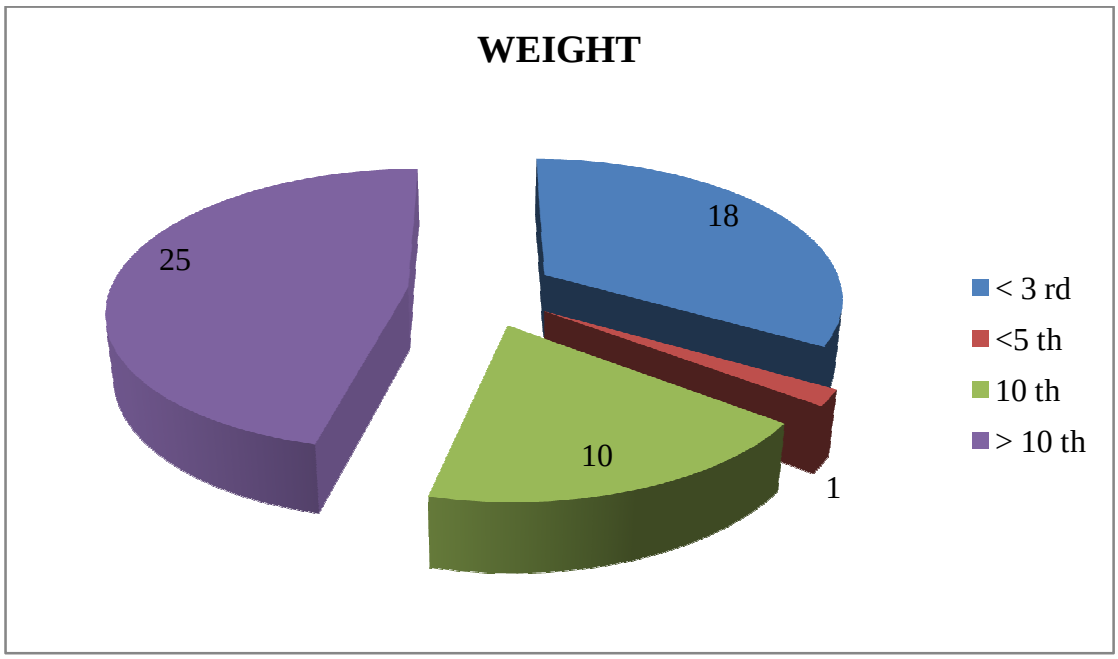
In this study, 57% had normal/carrier siblings and 12% had sibling death in family while one child of TI was on blood transfusion.

Height



In this study, there were 16 patients who had height less than 3 SD , and 38 patients height was more than 3 SD .

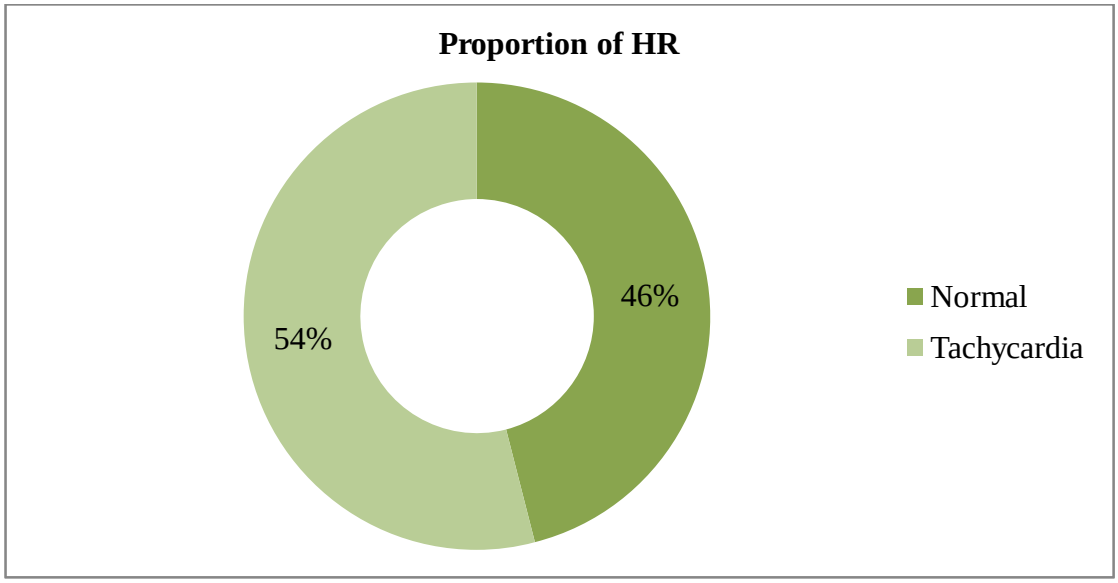
Weight



In this study, 33%(n=18) had weight < third centile, 19 % (n=10) had weight <10 centile.

Heart Rate

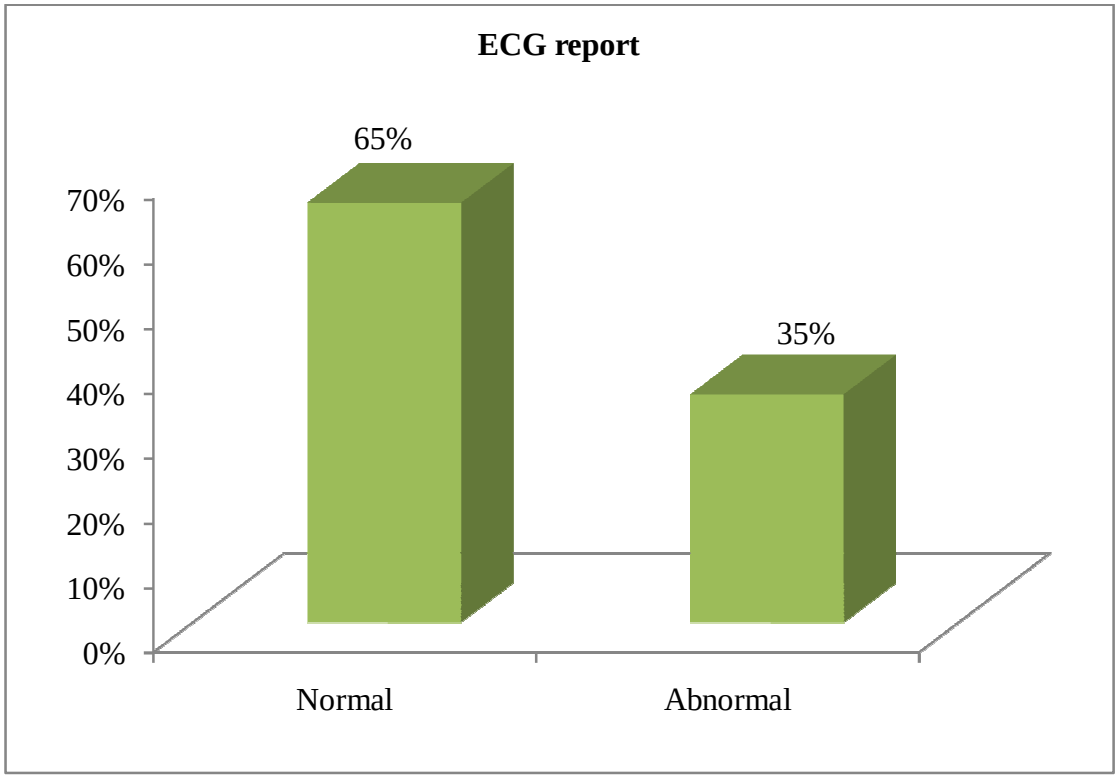
HR	N	Percentage
Normal	25	46%
Tachycardia	29	54%
Total	54	100%



In this study, 54% (n=29) patient had tachycardia at admission and 46% (n=25) had normal heart rate at admission.

ECG findings

ECG	No. of patients	Percentage
Normal	35	65
Abnormal	19	35
Total	54	100



In this study, 65% (n=35) had normal ecg and abnormal ecg was seen in 35 % (n=19) cases.

Serum Ferritin Level

SERUM FERRITIN (ng/dl)	No of patients	Percentage
<1000	13	24 %
>1000	41	76 %
Total	54	100

In this study, 24% (n=13) had normal ferritin level while 76% (n=41) cases had serum ferritin level more than 1000 ng/dl

Consanguinity			
Serum Ferritin (ng/dl)	**Consanguinity**	**Non consanguinous**	**Total**
<1000	4 (17%)	9 (30%)	13 (24%)
>=1000	20 (83%)	21 (70%)	41 (76%)
Total	24 (100%)	30 (100%)	54 (100%)

$\chi^2 = 0.67$, degree of freedom(df)=1, p=0.413(NS)

In the present study,there is no statistically significant association between serum ferritin level and consanguinity .

	Residence		
Serum Ferritin(ng/dl)	**Rural**	**Urban**	**Total**
<1000	9 (29%)	4 (17%)	13 (24%)
>=1000	22 (71%)	19 (83%)	41 (76%)
Total	31 (100%)	23 (100%)	54 (100%)

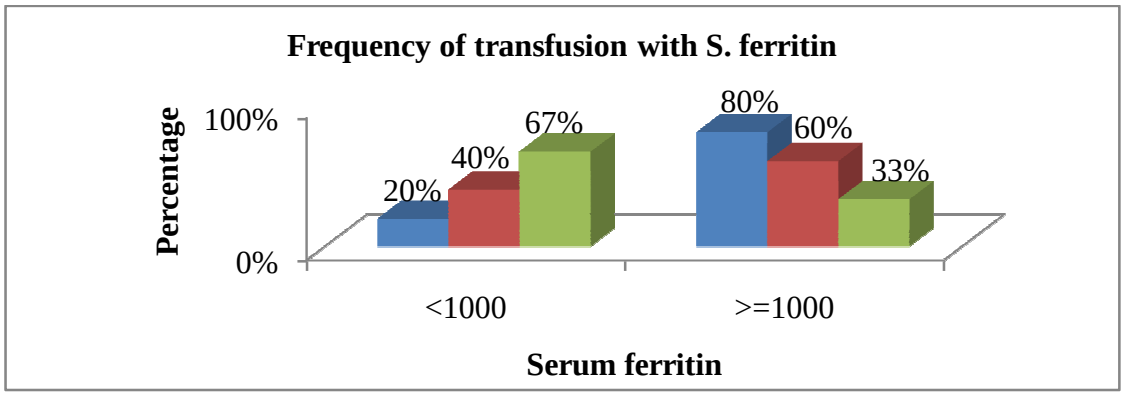
$\chi 2 = 0.446$, degree of freedom(df)=1, p=0.504(NS)

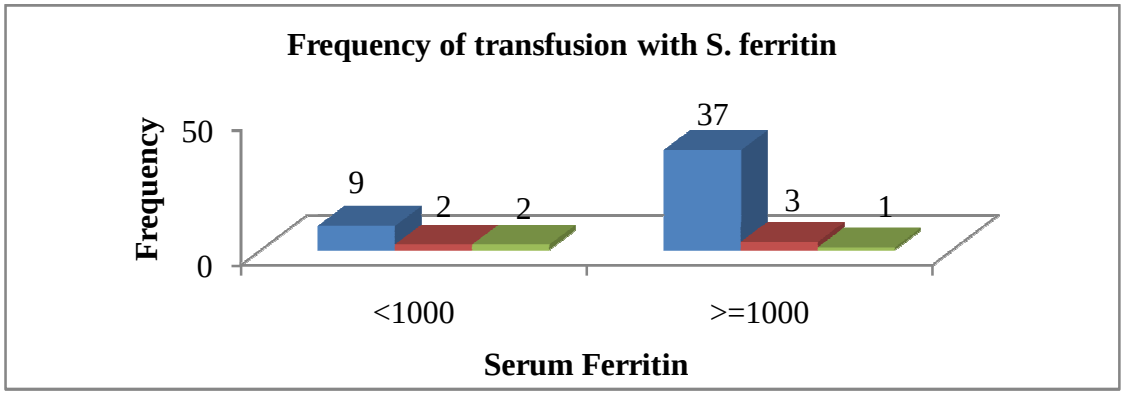
In the present study,there is no statistically significant association between serum ferritin level and geographical distribution.

Frequency of transfusion with S. ferritin

Frequency of transfusion				
Serum Ferritin (ng/dl)	**1**	**2**	**3**	**Total**
<1000	9 (20%)	2 (40%)	2 (67%)	13 (24%)
>=1000	37 (80%)	3 (60%)	1 (33%)	41 (76%)
Total	46 (100%)	5 (100%)	3 (100%)	54 (100%)

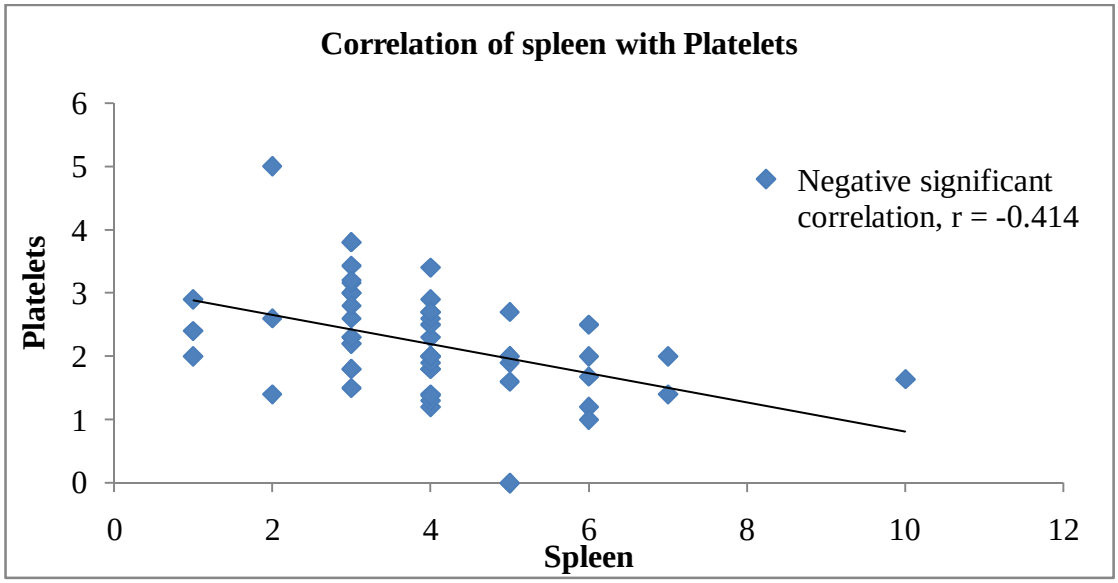
$\chi 2 = 4.2$, degree of freedom(df)=2, p=0.088(NS)





Monthly Once in 2 Months Once in 3 Months

In the present study, there is no statistically significant association between serum ferritin level and frequency of transfusions .it means that serum ferritin level is not a good indicator of chronicity of blood transfusions.



In the present study, low platelet counts had negative correlation with increase in spleen size.

Electrocardiography

	RVH		
Serum Ferriti (ng/dl)	**+**	**NIL**	**Total**
>=1000	3	35	38
	75.00%	81.40%	80.90%
<1000	1	8	9
	25.00%	18.60%	19.10%
Total	4	43	47
	100.00%	100.00%	100.00%

Pearson Chi-Square **p value** 0.756 (NS)

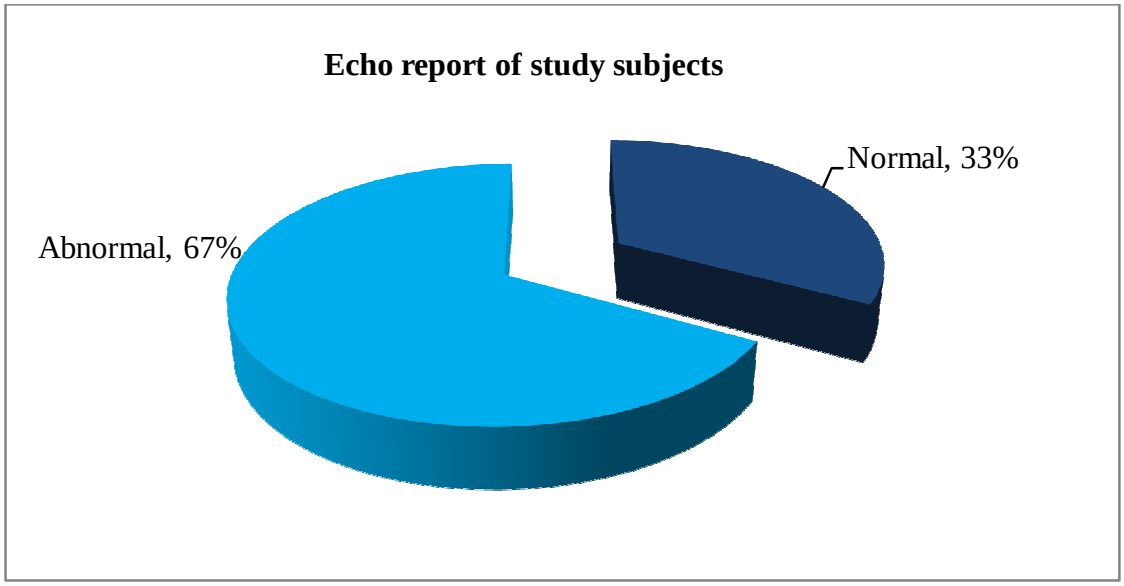
In our study, RVH was seen in total of 8.5% (n=4) patient with thalassemia major. Among these serum ferritin level was high in 75% (n=3) and normal in 25%. Serum ferritin level had no association with RVH as p value not statistically significant.(p value 0.756)

	LVH		
Serum Ferritin (ng/dl)	**+**	**NIL**	**Total**
>=1000	16	22	38
	93.80%	73.30%	80.90%
<1000	1	8	9
	6.20%	26.70%	19.10%
Total	17	30	47
	100.00%	100.00%	100.00%

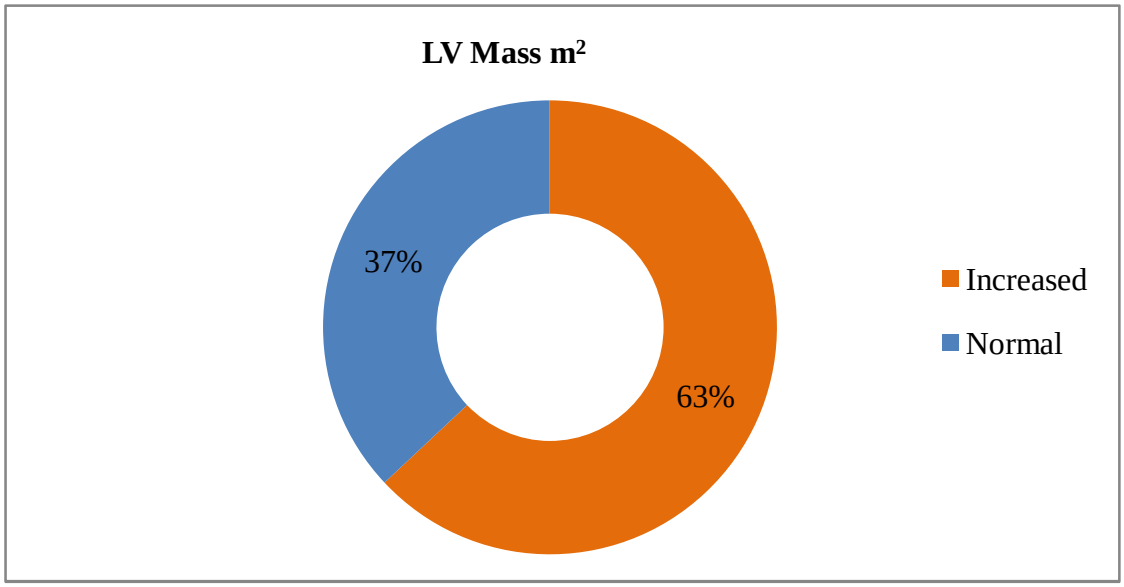
Pearson Chi-Square P value=0.217(NS)

In this study, 36% (n=36.1) 17 patient of total 47 thalassemia patient had LVH in ECG. Out of 17 patient 93.8 %(n=16) had serum ferritin level more than 1000ng/dl. Serum ferritin level had no association with LVH as p value not statistically significant. (p value=0.217)

Echocardiogram



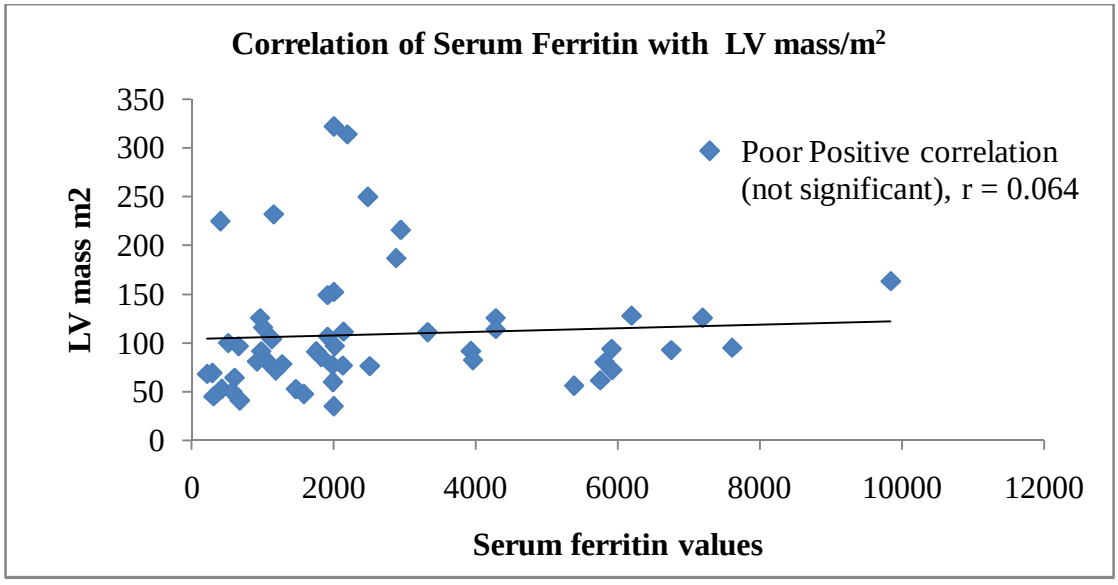
In this study echo was normal in 33 % and abnormal echo findings was seen in 67% of patient.



In this study, 63 % of patient showed increased LV mass/m^2 in echo and 37 % who had normal LV mass/m^2

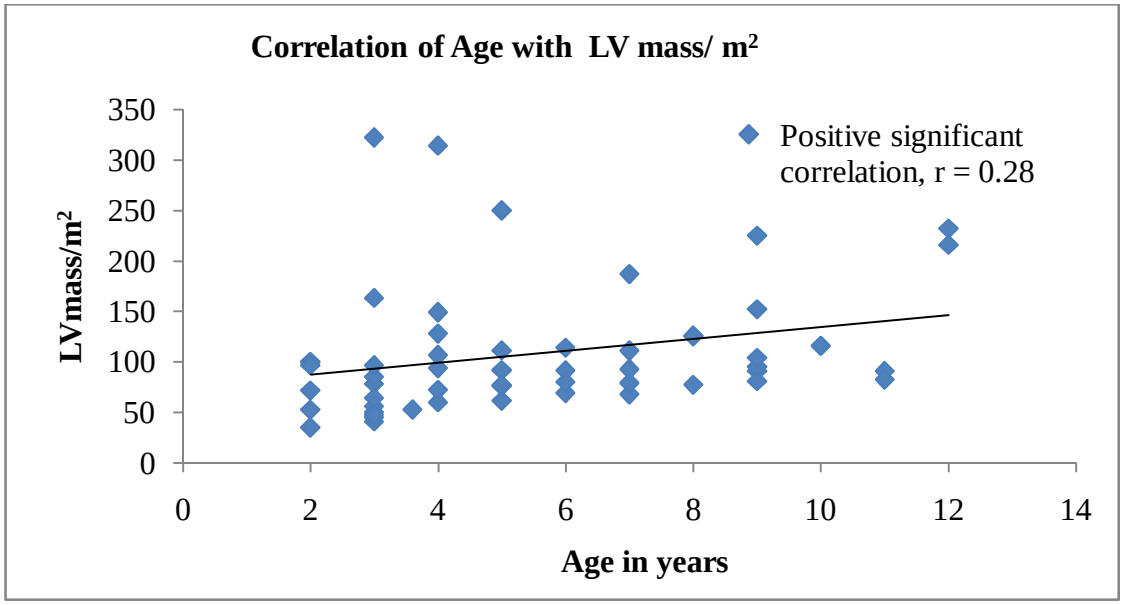
Correlation of Serum Ferritin with LV mass/m^2

Serum Ferritin (ng/dl)	LV mass/m^2
Sample size (N)	54
Pearson Correlation r	0.064
p value	0.645
Interpretation	very weak positive correlation



In this study, it is found that there is poor positive correlation of LV mass with the serum ferritin level.

Correlation of Age with LV mass/m^2



In the present study it was found that there is a positive correlation, r = 0.28 .

Age (in years)	LV mass m^2
Sample size (N)	54
Pearson Correlation r	0.282
p value	0.041*
Interpretation	Poor positive Significant correlation

In this study, it is found that there is poor positive correlation of LV mass/m^2 with the age and p value was significant less than 0.041.

Ejection fraction

EJECTION FRACTION (Normal- 56% TO78%)	No.of patients	Minimum	Maximum	Mean	Std. Error	Std. Deviation
	54	55	82	69.96	0.767	5.637

The mean Ejection fraction in our patients was 69.96%

Tr Velocity

Tr velocity	**EF**	**LV mass/m^2**
N	54	54
Pearson Correlation	-0.10	0.258
p value	0.477	0.06
Interpretation	Weak negative correlation	Poor positive correlation

In this study , it seen that there poor positive correlation between LV mass and TRV. There is poor negative correlation between EF and TRV. It indicates that right and left ventricular dysfunction can occur independently.

Serum Ferritin / Echo Findings

	Serum ferritin (ng/dl)		
LV mass/m^2	>=1000	<1000	Total
INCREASED	27	3	30
	71.10%	33.30%	63.80%
NORMAL	11	6	17
	28.90%	66.70%	36.20%
Total	38	9	47
	100.00%	100.00%	100.00%

Pearson Chi-Square **p value** 0.034 (significant)

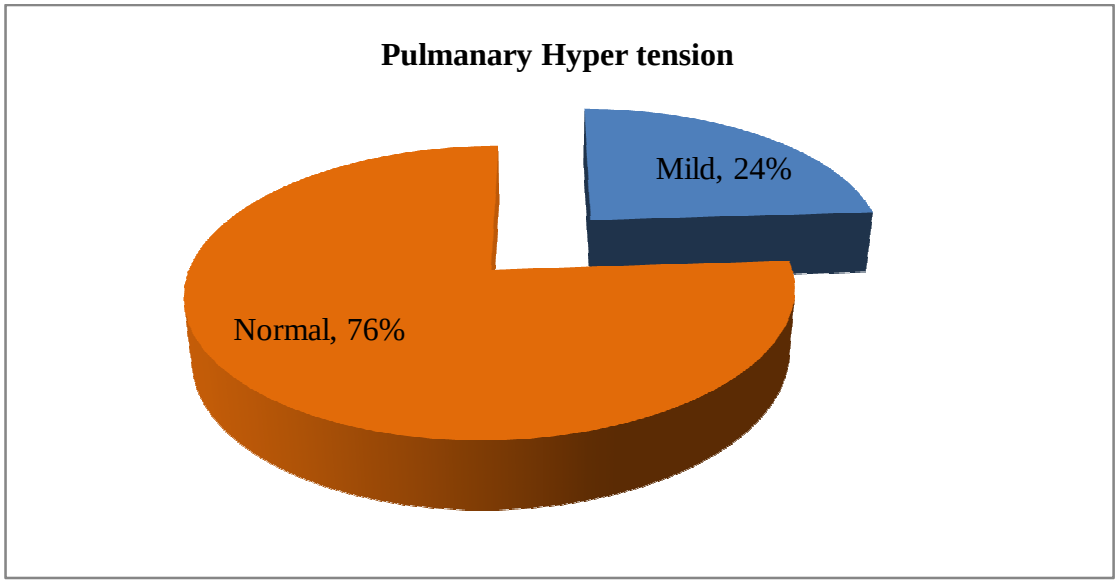
In our study, 38 thalassemia major patients serum ferritin level was more than 1000ng/dl. In these cases LV mass/m^2 was increased in 71.1 % and had 28.9 % cases had normal LV mass/m^2 inspite of increased serum ferritin level. 3 patient with thalassemia major who had serum ferritin level below 1000ng/dl had increased LV mass. This was statistically significant.

	Echocardiogram		
LV mass	Abnormal	Normal	Total
INCREASED	29	1	30
	90.60%	6.70%	63.80%
NORMAL	3	14	17
	9.40%	93.30%	36.20%
Total	32	15	47
	100.00%	100.00%	100.00%

Continuity Correction Chi square value p value 0.0001(highly significant)

In our study, out of 47 thalassemia major patient 32 patient had abnormal echo findings which was statistically significant.

Pulmanary Hyper tension



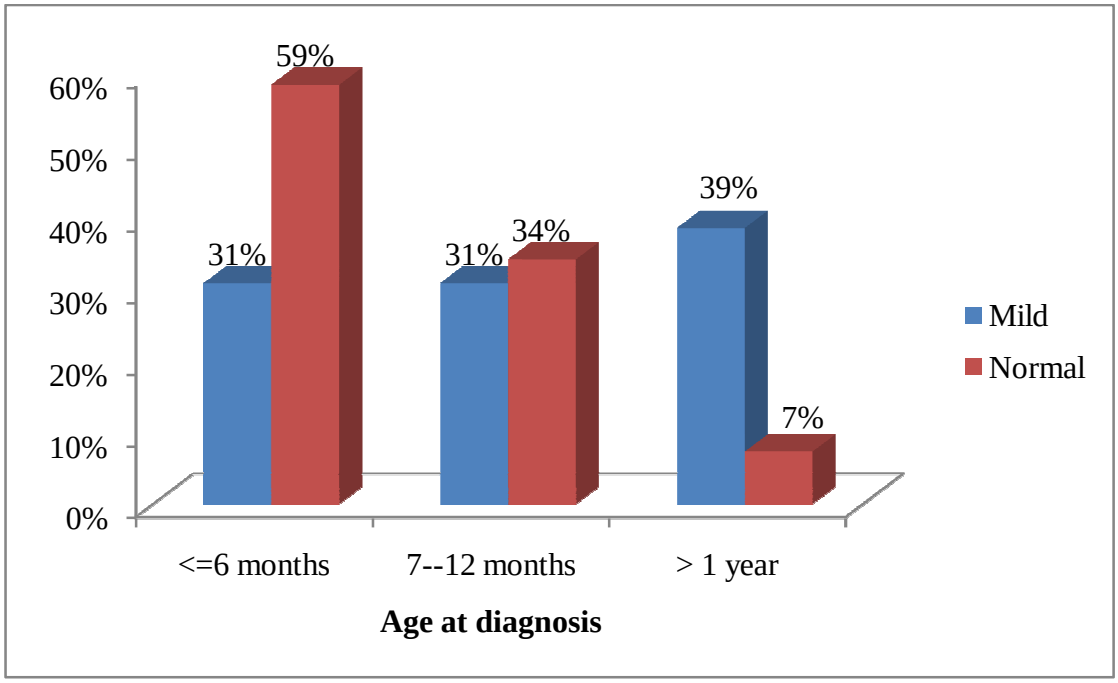
In this study, pulmonary hypertension was seen in 24 % of patient and 76% did not show evidence of pulmomary hypertension in echo.

Relation of Age at Diagnosis and Pulmonary Hypertension

	Pulmonary hypertension		
Age at diagnosis	Mild	Normal	Total
<=6 months	4 (31%)	24 (59%)	28 (52%)
7--12 months	4 (31%)	14 (34%)	18 (33%)
> 1 year	5 (38%)	3 (7%)	8 (15%)
Total	13 (100%)	41(100%)	54 (100%)

*Significant at P<0.05

$\chi 2 = 7.964$, degree of freedom(df)=2, p=0.019 (Significant)

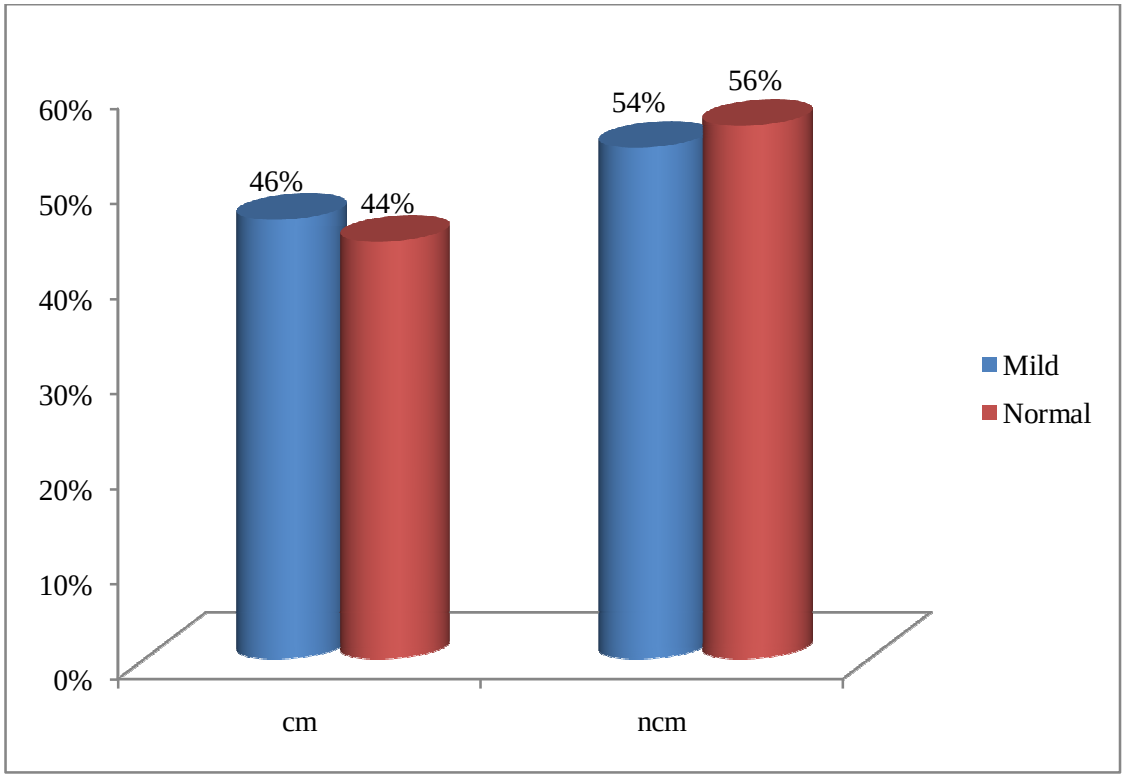


In the present study, the incidence of pulmonary hypertension showed statistically significant association with the age of diagnosis of thalassemia (p value = 0.019)

Pulmonary hypertension with Consanguinity

	Pulmonary hypertension		
Consanguineous	Mild	Normal	Total
cm	6 (46%)	18 (44%)	24 (44%)
ncm	7 (54%)	23 (56%)	30 (56%)
Total	13 (100%)	41 (100%)	54 (100%)

$\chi 2 = 0.081$, degree of freedom(df)=1, p=0.887 (NS)

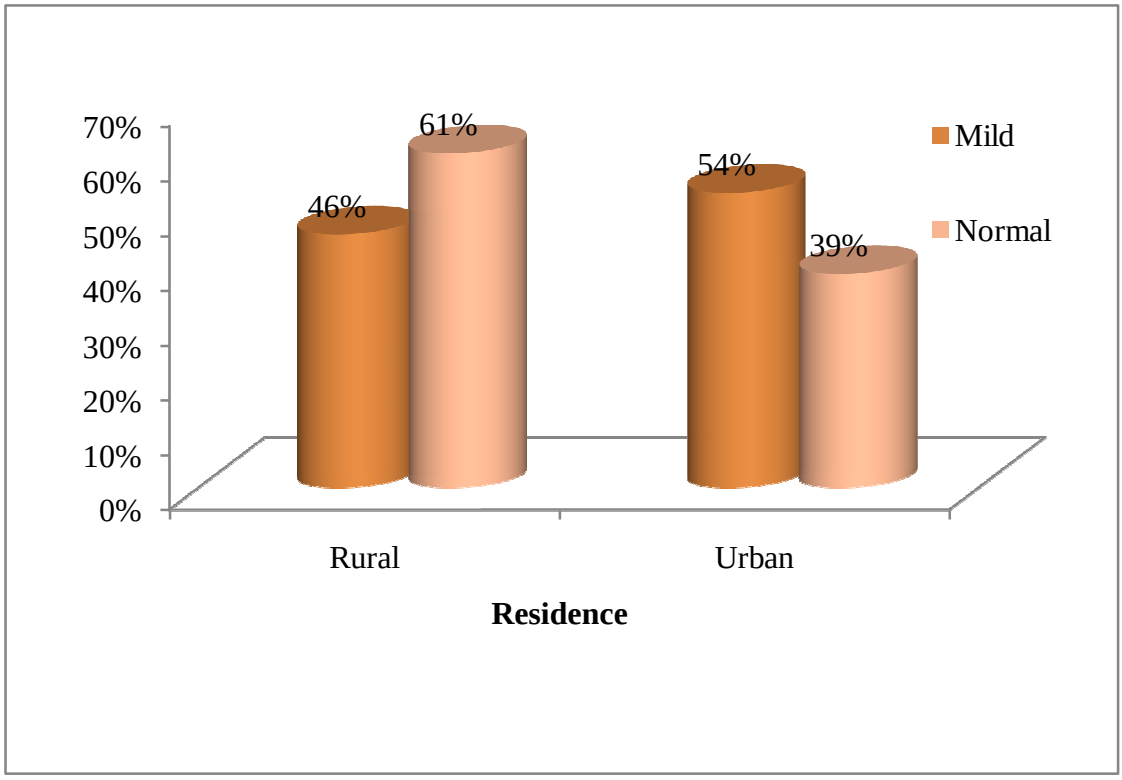


In this study, incidence of pulmonary hyptertension did not show any statistically significant association with the type of marriage. (p value =0.887)

Pulmonary Hypertension with Residence

	Pulmonary Hypertension		
Residence	Mild	Normal	Total
Rural	6 (46%)	25 (61%)	31 (57%)
Urban	7 (54%)	16 (39%)	23 (43%)
Total	13 (100%)	41(100%)	54 (100%)

$\chi 2 = 0.081$, degree of freedom(df)=1, p=0.535 (NS)

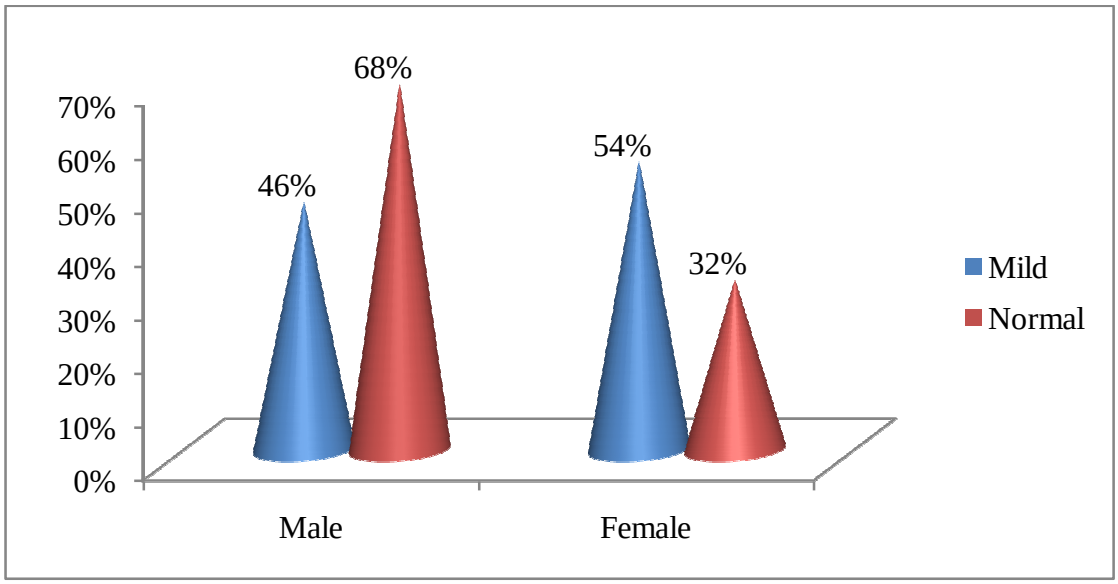


In this study, incidence of pulmonary hypertension did not show any statistically significant association with the area of residence (p value =0.535)

Pulmonary hypertension with Gender

	Pulmonary hypertension		
Gender	Mild	Normal	Total
Male	6 (46%)	28 (68%)	34 (63%)
Female	7 (54%)	13 (32%)	20 (37%)
Total	13 (100%)	41 (100%)	54 (100%)

$\chi 2 = 1.234$, degree of freedom(df)=1, p=0.267 (NS)



In this study, incidence of pulmonary hypertension did not show any statistically significant association with the sex of patient (p value =0.267)

Right Heart Functions with Serum Ferritin

	Pulmonary hypertension		
Serum Ferritin (ng/dl)	Mild	Normal	Total
>=1000	10	28	38
	100.00%	74.30%	80.90%
<1000	0	9	9
	0.00%	25.70%	19.10%
Total	10	35	47
	100.00%	100.00%	100.00%

Pearson Chi-Square P value=0.148(NS)

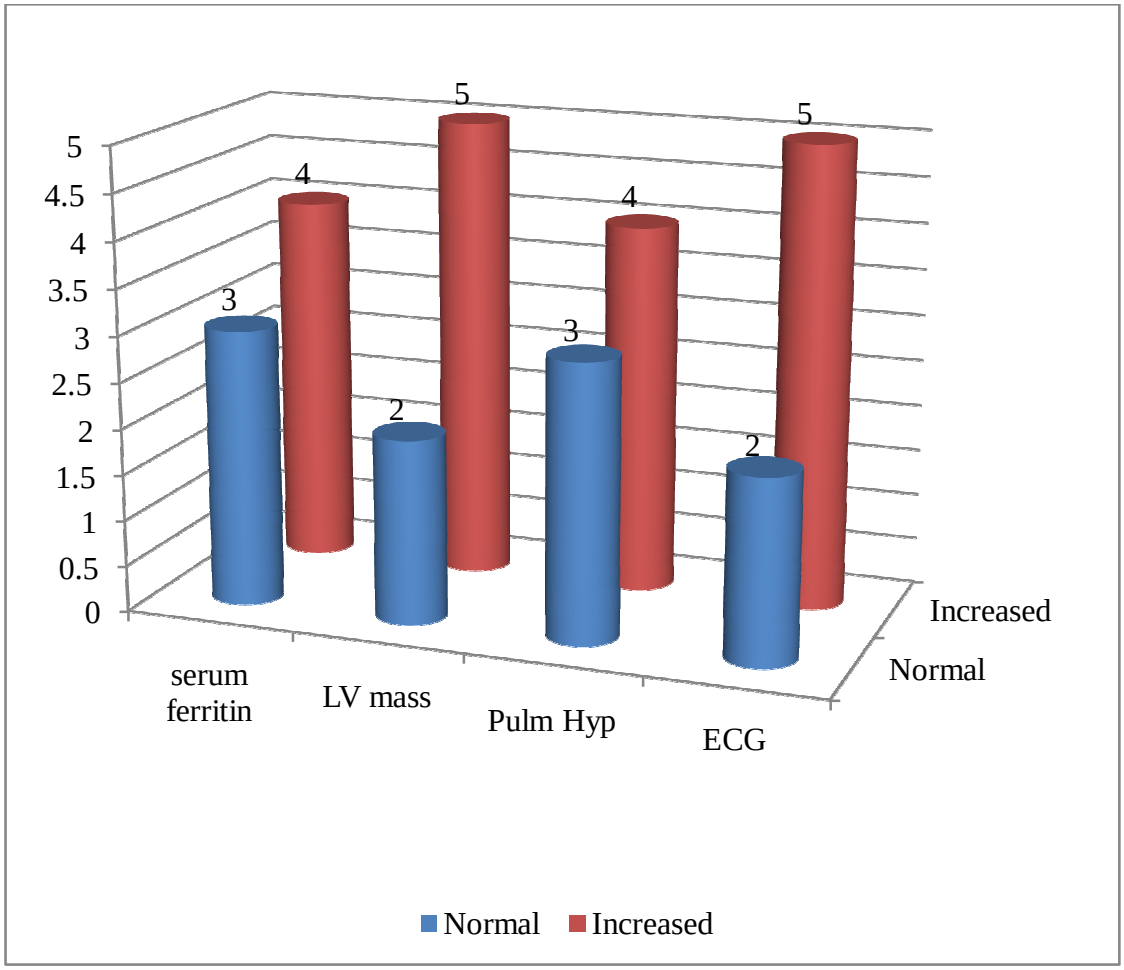
In this study, 21.2%(n=10) thalassemia major cases had pulmonary hypertension . All these patients had serum ferritin level more than 1000 ng/dl. Pulmonary hypertension and serum ferritin level have no association as p value is 0.148.

	Tricuspid regurgitation			
Serum Ferritin (ng/dl)	Mild	Normal	Trivial	Total
>=1000	10	17	11	38
	90.90%	66.70%	78.60%	80.90%
<1000	1	5	3	9
	9.10%	33.30%	21.40%	19.10%
Total	11	22	14	47
	100.00%	100.00%	100.00%	100.00%

Pearson Chi-Square P value=0.623(NS)

In this study, out of total 47 thalassemia major patient 22 patient did not have tricuspid regurgitation. Serum ferritin level did not show any association with trisupid regurgitation as p value 0.623.

Thalassemia Intermedia (7 Patients)



In the graph we can see that LVmass is increased in 71% (n=5) of thalassemia intermedia patients and 57% (n=4) had pulmonary hypertension. Also serum Ferritin was increased in 57% (n=4) patients '

Chi-square test is not used as the sample size was small.

SENSITIVITY ANALYSIS

	ECG		
Echo	**Abnormal (+ve)**	**Normal (-ve)**	**Total**
Abnormal (+ve)	17	19	36
Normal (-ve)	2	16	18
Total	19	35	54

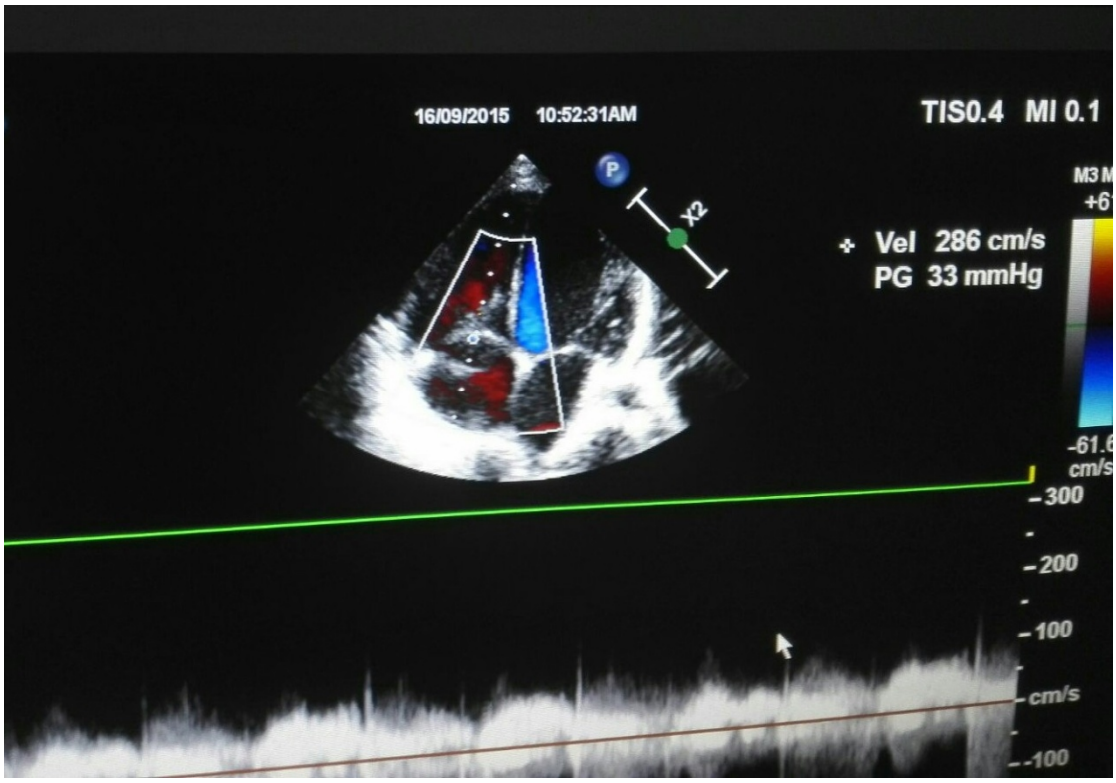
Parameter	**Estimate**	**Lower - Upper 95% CIs**
Sensitivity	89.47%	(68.61, 97.06[1])
Specificity	45.71%	(30.47, 61.81[1])
Positive Predictive Value	47.22%	(31.99, 62.99[1])
Negative Predictive Value	88.89%	(67.2, 96.9[1])
Diagnostic Accuracy	61.11%	(47.79, 72.96[1])

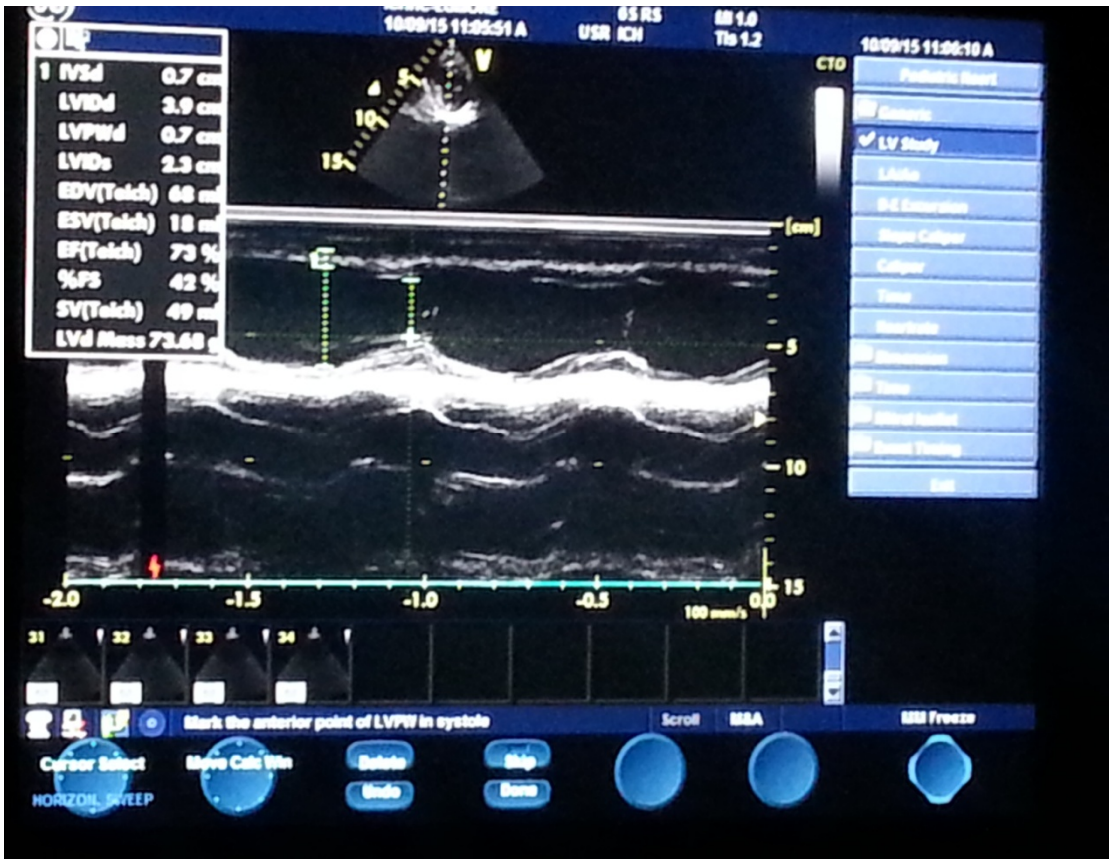
1 Wilson score method

The sensitivity of echo in comparison with ecg in detection of any cardiac complication in thalassemia patient on chronic blood transfusion was 89.47 % and specificity was 45.71% .The negative predictive value of echo is 88.89 % (CI 95%)

This can prove that 2 D echocardiography is more sensitive and as the negative predictive value is high. We can exclude any cardiovascular complication arising from chronic blood transfusion using 2 D echocardiography as initial screening tool.

Pictures of Echocardiography in Thalassemia Patients





DISCUSSION

This study was conducted at Institute of Child Health and Hospital for Children, Chennai, from June 2015 to October 2015.

We included 54 patients of β thalassemia who were transfusion dependant, to study the significance of echocardiography in them. Children more than 2 years of age and less than 12 years were part of the study. Children who had a congenital heart disease and those with the terminal illness were excluded from the study.

Majority of the studies on cardiovascular complications done in the Mediterranian region and the South East Asia were in the age group who are more than ten years. In our study, all the patients were less than twelve years of age. 63%(n=34) were less than 6 years and 37%(n=20) between 6 and 12 years.

In studies by Samira Z sayed et al, Noor mohammad Noori et al patients were more than ten years of age and A, Azarkeivan etal had patients more than seven years of age. It was seen in these studies that cardiac complications occur early inspite of regular blood transfusions and in well chelated patients.

Gender	**Present study**	**Samira Z Sayed et al**	**Ameen mosa et al**
Male	63%	64%	49%
Female	37%	36 %	51%

In the present study 63% (n=34) of the patients were males and 37% (n=20) females respectively. There are other studies done by Samira Z Syed etal (male -64%. Females-36%) and Ameen mosa etal (male-49% , females-51%) where similar male preponderance was seen. Though the probability of the child inheriting the disease(autosomal recessive disorder) does not show sex predilection, it is seen more commonly in boys in few of the studies.

In our study, 44 % (n=24) were born to consanguineous parents and 56%(n=30) of them to non consanguineous parents. It implies that the parents of the proband are heterozygous and obligate carriers reflecting the high frequency of carriers in the population. It can be due to de novo mutations also.

It is important as the relatives of carriers should also be screened and genetic counseling and premarital testing can prevent these births.

A similar study by Samira Zyed et al in showed that around 32 % of the thalassemia patients were from consanguineous marriage , and 67.8 % were from non consanguineous marriage, where the prevalence is high.

Out of the 54 patients, 47 of them had thalassemia major and the remaining intermedia confirmed by hemoglobin electrophoresis.

Age at diagnosis	**Present study**	**Samira Z Sayed et al**	**Ameen mosa et al**
Minimum age at diagnosis	3 months	6 months	6 months
Mean	9.4 months	8- 9 months	6-9 months

The minimum age at diagnosis of thalassemia in our study was 3 months, in comparison to 6 months in Samira Zyed etal and Ameen mosa et al study. As most of the affected thalassemia children present in infancy at around six months of age,this finding is significant as these children were screened for thalassemia after the death of their elder siblings.However the mean age of diagnosis 9.4 month as seen in the other studies

Sibling history in our study showed that 57% (n=27) had an asymptomatic carrier/ normal child in the family. Whereas 24% (n=13) of the thalassemia patients in our study were being reared as a single child because the other pregnancy was terminated due to antenatal screening being positive .

19 % (n=10) of these patients had a sibling who was affected with TM, of which only 7%(n=4) were alive, on transfusions, but 12%(n=6) had lost their brother or sister due to the disease or its complications .

Geographical Area	**Present study**	**Samira Z Sayed et al**
Urban	57 %	29%
Rural	43%	71%

In the present study 57% (n=) of the patients were from urban set up and 43%(n=) from rural area. However this is not of significance as both the groups were on regular transfusions.

Frequency of transfusion:

In our study 85% (n=47) of patients of thalassemia major were on regular blood transfusions once a month. 9% (n=5) of patients of TI were on blood transfusions once in two months and the remaining 6%(n= 2) patients once in 3 months respectively.

Weight in kg	**Present study**	**Samira Z Sayed et al**
< 5 percentile	33%(n=18)	35.7%
5-95 centile	19%(n=10)	64.3%
Mean weight	15.98	23

In this study, 33% of the thalassemia patients had weight < third centile, i.e these patients were under weight and one third of the patients were malnourished. Similarly 30% of these patients, also had short stature.

54% (n=29) of our patients had tachycardia and 46 % (n=25) had normal heart rate for the age. This is secondary to anemia, mean hemoglobin in these patients was 7.34gm/dl

Mean EF was 70% and fraction shortening was 39.54.mean LVMI in these patients was 79.63 gm/m^2.

Similar results was seen in study by Samira Z etal, Noor Mohammad Noorietal and others. Chronic anemia causes increase in volume overload and heart rate.

Patients of thalassemia have a heart rate that is higher than the normal people for the corresponding age.

All 54(100%) patients in our study had systolic and diastolic blood pressure less than the 95th centile when plotted on NHBPEP charts for their corresponding age and sex. Systemic blood pressure is well maintained in these patients. Study by Sara and S Dru Foote al observed that even patients with pulmonary hypertension had normal systemic blood pressure.

Hemoglobin at admission

Hb (gm%)	Present study	Mosa et al
Mean Hb	7.33	9
Low Hb	6	7.9

Mean hemoglobin values in our study was 7.33gm/dl. Low hemoglobin values may be the cause for pulmonary hypertension in these patients. Chronic anemia can cause growth retardation also. In a study by Mosa etal and Sara et al mean hemoglobin was 9gm/dl.

Serum ferritin level

	Present study	Samira Z Sayed et al
< 1000 ng/dl	24 %	-
>1000ng/dl	76%	100%

In our study patients were further classified based on the serum ferritin value into those who had values more than 1000ng/ml and the ones with less than 1000ng/ml to know the extent of iron overload. Inspite of being on oral

chelators three fourth of the study population had serum ferritin more than 1000ng/ml and only 24%(n=13) had values less than 1000ng/ml.

Patient with least value of 215ng/ml had TI, on transfusions once in three months. 4 out of 7 of TI patients had ferritin lower than 1000ng/ml and 3 of them higher. Frequency of blood transfusions in TI patients is less than TM patients.

Patients with low values of ferritin had an average of total of 30 transfusions.

Serum ferritin values were compared with the chest xray, ecg and echocardiography findings to know the relation between cardiac function and iron overload.

Of the 47 TM patients , 19%(n=9) , had serum ferritin values lower than 1000 ng/ml whereas 80.90%(n=38) had serum ferritin values more than 1000ng/ml. Out of the 38 patients with high ferritin values only 75% of them had RVH on ecg. Statistically no association was found with serum ferritin and ecg finding of RVH as p value was 0.756. Similarly serum ferritin had no association with LVH in ecg. But it was observed that 93% out of 38 patients of TM had LVH in ecg.

In our study , 35 patients out of 54 had cardiomegaly on chest x ray, but only 77%(n=27) of these patients had high serum ferritin values which means that cardiomegaly in these patients can be due to chronic anemia and volume overload rather than iron overload alone. Qtc interval was in the normal range

in all patients. Electrocardiography did not show arrhythmias. Unlike the study by Samira et al where QTc and QTd was increased significantly in patients with serum ferritin level more than 5000ng/ml.

Echocardiography showed that 10 out of 47 patients of TM had mild pulmonary hypertension and all these 10patients (100%) had serum ferritin more than 1000ng/ml.

In our study, 38 out of 47 patients of TM had serum ferritin values more than 1000ng/ml and 71.10% (n=27) had increased LVmass. However serum ferritin had poor positive correlation with LV mass and pulmonary hypertension, hence it cannot be used as single marker for cardiac iron load in transfusion dependant thalassemia patients.

Ejection fraction: it was found to be mildly elevated than the normal values for age.

	Present study	Samira Zet al	Mosa et al	A Azar et al
Mean	69.96%	66.28%	65%	60 %
Range	55% to 82%	62.3%to 70.12%	56-65 %	60.3±9.7%

LV mass

LV mass and LV mass index was increased in 63% (n=34) of the total patients i.e these children had LV mass and LVMI more than 95th centile for the corresponding age and sex in normal children. And 37%(n=20) had less than 95th centile for the corresponding age and sex when plotted on the age specific reference intervals for indexed left ventricular mass in children.

Similar findings were observed in other studies done by two separate studies by Noor mohammad et al. LVmass and LV mass index was seen increased in these studies done by Assad Abdullah Abbas etal, Ameen Mosa et al and Samira Z Sayed etal.

Chronic anemia, tissue hypoxia and iron overload are some of the causes of increase in LVmass and LVmass index thalassemia.

Increase in LV mass and LV mass index in thalassemia is multifactorial. It is due to chronic anemia, tissue hypoxia and iron overload.

The dimensions used for calculating the LV mass like LVIDd, LVIDs, interventricular septal thickness and posterior wall thickness of ventricular wall was also observed to be increased in these patients above the average normal levels.

Similar observations were seen in study by Ameenmosa et al, Samira Z Sayed et al.

Pulmonary hypertension was seen in 24% of 54 patients in our study.76.9% (n=10) of these patients were of TM and 23% (n=3) were of TI respectively. However p value was not significant. But 42% of TI patients and 21 % of TM patients had pulmonary hypertension. This shows that incidence of PH is more in TI than TM. Sylvia[28] et al also observed in their study that high prevalence of pulmonary hypertension is seen in well transfused TM patients and most importantly in TI patients

8(62%) out of 13 children with pulmonary hypertension were diagnosed to have thalassemia in their infancy. 41 children did not have pulmonary hypertension. This was statistically significant as p value was 0.019.

This implies that incidence of thalassemia intermedia is high as the age advances. However it had no association with consanguinity, geographical distribution, or sex of the patient.

Mean hemoglobin in patients with pulmonary hypertension was 7.4%and the mean age in these children was 5.38 years.

In a study by Meloni etal it was seen that low risk of pulmonary hypertension was found in well transfused thalassemia major patients than thalassemia intermedia.

Sylvia etal at Childrens Hospital Oakland Research Institute, California, also had high prevalence of PH in TI and in well transfused TM patients. These patients also had low hemoglobin and high serum ferritin levels than those who did not have pulmonary hypertension[28].

The sensitivity and specificity of echocardiography on thalassemia patients in our study when compared to ecg was found to be 89.47% and specificity was 45.7%. Negative predictive value was 89%.

As Echocardigraphy findings was not compared with MRI, the efficacy of this procedure in confirming cardiac iron load is less. And hence T2* MRI is the gold standard in diagnosis of cardiac iron deposition. Further pulmonary hypertension should also be confirmed by cardiac catheterisation.

Serum ferritin is not an indicator of cardiac iron overload.

Hence echocardiography combined with electrocardiogram can be used for regular periodic follow-up. Complications can be prevented in early in asymptomatic children.

Even though mortality secondary to cardiac complications is seen in second decade, the pathologic changes occur in first decade only. This should be diagnosed early by easily available, affordable, non invasive technique like echocardiography.

Echocardiography combined with electrocardiogram should be used for regular periodic monitoring of transfusion dependent thalassemia patients.

CONCLUSIONS

- Cardiac complications can occur in first decade also secondary to chronic anemias and iron overload.
- 24 % of our thalassemia major patients have pulmonary hypertension.
- 63 % of our thalassemia patients had increased LV mass which was > 98 percent of the age matched reference values.
- Cardiac arrhythmias considered as the most common cause of death in thalassemia patients is not found in our patients. (< 12 years).
- Serum ferritin value did not correlate with the cardiac abnormality found in echocardiography, hence Cardiac M RI which is considered as gold standard should be used.

LIMITATIONS

- Being an institutional based study the findings cannot be projected at a community level.
- Small sample size
- All parameters of cardia have to be evaluated in echocardiography and compared with MRI and normal controls.

RECOMMENDATIONS

- Echocardiography can be used for screening of cardiac complications in children less than ten years of age and followed up periodically.
- As serum ferritin does not correlate with the cardiac iron overload and dysfunction, T 2 MRI which is the gold standard should be used..
- Importance of early involvement of cardia in thalassemia patients should be conveyed to all treating paediatricians.
- Combination chelation therapy can be used in patients with cardiac toxicity secondary to iron overload
- In addition to prenatal diagnosis for thalassemia , pre marital screening should be offered at the community level.

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ABBREVIATIONS

RDW	-	Red Cell Distribution Width
CVS	-	Chorionic Villous Sampling.
PUBS	-	Percutaneous Umbilical Cord Blood Sampling
TM	-	Thalassemia Major
TI	-	Thalassemia Intermedia
DNA	-	Deoxy Ribonucleic Acid
ECG	-	Electrocardiogram
PH	-	Pulmonary Hypertension
Hb	-	Hemoglobin
m RNA	-	Messenger Ribose Nuceic Acid.
LV Mass	-	Left Ventricular Mass
BP	-	Blood Pressure
IVS	-	Inter Ventricular Septum
PWT	-	Posterior Wall Thickness

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
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CERTIFICATE OF APPROVAL

To
Dr. Usha B K
Post Graduate in M.D. (Paediatrics)
Institute of Child Health and Hospital for Children
Madras Medical College
Chennai 600 003

Dear Dr. Usha B K

The Institutional Ethics Committee has considered your request and approved your study titled **"A Study of Significance of Echocardiography in Thalassemia Major/Intermedia Patients Attending a Tertiary care centre". No.10072015.**

The following members of Ethics Committee were present in the meeting held on 07.07.2015 conducted at Madras Medical College, Chennai-3.

1.	Prof.C.Rajendran, M.D.,	: Chairperson
2.	Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3.	Prof.Sudha Seshayyan, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4.	Prof.B.Vasanthi, M.D., Professor Pharmacology, MMC	: Member
5.	Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC	: Member
6.	Prof.Md.Ali, M.D., D.M., Prof. & HOD of Medl.G.E., MMC	: Member
7.	Prof.Baby Vasumathi, Director, Inst.of O&G, Ch-8	: Member
8.	Prof.K.Ramadevi, Director, Inst.of Biochemistry, MMC	: Member
9.	Prof.Saraswathy, M.D., Director, Inst. Of Pathology, MMC	: Member
10.	Prof.Srinivasagalu, Director, Inst.of Inter Med. MMC	: Member
11.	Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
12.	Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
13.	Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

9/9/15
Member Secretary, Ethics Committee
MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE

ANNEXURES

INFORMATION SHEET

Place of study: INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN, GENERAL OPD

Name of Investigator : DR. USHA B K

Name of Participant age: sex:

Hospital No:

Study title : Study of Echocardiography in thalassemia(major/ intermedia) patients at tertiary care centre , ICH&HC , Chennai.

- We are conducting a study of echocardiography in thalassemia(major/intermedia) patients at tertiary care centre, ICH & HC, Chennai.
- Thalassemia is an inherited hemoglobin disorder caused by impaired synthesis of the beta –globin chain and resulting in hemolytic anemia.
- Depending on clinical severity , two forms thalassemia major and intermedia are defined. Cardiac complications are a main feature of the clinical spectrum of beta thalassemia. Despite adequate iron chelation , myocardial dysfunction is due to iron deposition, fibrosis, and chronic anaemia.
- We are conducting a study in ICH & HC regarding study of echocardiography in thalassemia (major/ intermedia) patients in tertiary care centre ICH&HC, Chennai.

We request you to participate in the study

- The purpose of this study is to compare rapid screening tests with gold standard urine culture test for diagnosing urinary tract infection.
- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.
- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.
- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator Signature of participant

Date:

INFORMED CONSENT FORM

Study place: INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN

Title of the study: Study of Echocardiography in thalassemia (major/intermedia) patients at tertiary care centre,ICH&HC,Chennai.

Name of the investigator : DR. USHA B K

Name of the Participant: Age: Sex:

Hospital number:

1. I have read and understood this consent form and the information provided to me regarding the participation in the study.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have informed the investigator of all the treatments I am taking or have taken in the past including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer
   unusual symptoms. *
8. I have not participated in any research study in the past.
9. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *
10. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *
11. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
12. I understand that my identity will be kept confidential if my data are publicly presented

13. I have had my questions answered to my satisfaction.

14. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing

This consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document. For adult participants:

Name and signature / thumb impression of the participant /parents/guardian

Name _____ Signature_____
Date_____

Name and Signature of impartial witness:

Name _____ Signature_____
Date_____

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____
Date_____

ஆராய்ச்சியில் பங்கு பெறுவோர்கான தகவல் படிவம்

ஆராய்ச்சி நடத்தப்படும் இடம் : அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை-8.

முதன்மை ஆராய்ச்சியாளர் : டாக்டர் உஷா பிகே.

பங்கேற்பவர் பெயர்: வயது: பாலினம்:

மருத்துவமனை எண்:

ஆய்வின் தலைப்பு : அரசு குழந்தைகள் நல மருத்துவமனையில் அனுமதிக்கப்பட்டுள்ள தலசிமியா குழந்தைகளுக்கு, இதய மின் ஒலி வரைவியல் ஏற்படும் மாற்றங்களை பற்றிய ஆய்வு

நாங்கள் உங்கள் குழந்தையை இந்த ஆய்வில் பங்கெடுக்குமாறு கேட்டுக்கொள்கிறோம்

ஆய்வின் நோக்கம்:

தலசிமியா நோயினால் குழந்தைகளுக்கு ஏற்படும் இரத்த சோகை சரி செய்வதற்காக அடிக்கடி உடலில் இரத்தம் ஏற்றுவதினால் இதயத்தில் ஏற்படும் மாற்றங்களை மின் ஒலி வரைவியல் மூலம் கண்டறிவது.

மேலும் இரத்த சோகை மற்றும் அதிகபடியான இரும்பு தாது இதய திசுக்களில் வரும் விளைவுகளை கண்டறிவது.

செய்முறை:

உங்கள் குழந்தைக்கு இருக்கும் உடன் நோய்களை கண்டறிவதற்கு உங்களிடம் உங்களை பற்றியும், உங்கள் குழந்தையைப் பற்றியும், சில கேள்விகளை கேட்டு, உங்கள் குழந்தையின் எடை, உயரத்தை அளந்தும், குழந்தையை பரிசோதனை செய்தும், மருத்துவமனையிலிருந்து விடுவிக்கும் நாள் வரை குழந்தையை பின்பற்றுவோம்.

ஆய்வில் பங்கேற்க மறுத்தால்?

இந்த ஆய்வில் பங்கேற்பது முற்றிலும் உங்களது சொந்த விருப்பமே. தாங்கள் எப்பொழுது வேண்டுமானாலும் இவ்வாராய்ச்சியிலிருந்து விலகிக் கொள்ளலாம். தாங்கள் விலகி கொள்வதால் உங்கள் குழந்தைக்கு அளிக்கப்படும் சிகிச்சையில் எந்தவித மாற்றமோ, பாதிப்போ இருக்காது.

பங்கேற்பதின் இலாப, நஷ்டங்கள்

இந்த ஆய்வில் இருந்து பெறப்படும் தகவல்கள் நம் நாட்டை நோயில்லாத நாடாக மாற்ற உபயோகப்படும். இவ்வாறு நாட்டின் வளர்ச்சியில் பங்கேற்ற பெருமை உங்களையும், உங்கள் குழந்தையையும் சேரும்.

இரகசியத் தன்மை

ஆய்வில் இருந்து பெறப்படும் தகவல்கள் வெளியிடப்படும்பொழுது உங்கள் மற்றும் உங்கள் குழந்தையின் அடையாளம் இரகசியமாக வைக்கப்படும்.

பங்கேற்பவர் உரிமை

இந்த ஆய்வைப் பற்றி மேலும் தகவல் அறிய தொடர்பு கொள்ள வேண்டிய நபர்

முதன்மை ஆராய்ச்சியாளர் : டாக்டர் உஷா பி.கே.

கைபேசி எண் : 9094973733

முகவரி : இரண்டாம் ஆண்டு, முதுநிலை மருத்துவ மாணவர்
அரசு குழந்தைகள் நல மருத்துவமனை மற்றும்
ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை-8.

இடம்:

தேதி: பெற்றோர் கையொப்பம்

ஒப்புதல் படிவம்

ஆராய்ச்சி நடத்தப்படும் இடம் : அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை-8.

முதன்மை ஆராய்ச்சியாளர் : டாக்டர் உஷா பிகே.

பங்கேற்பவர் பெயர்: வயது: பாலினம்:

மருத்துவமனை எண்:

ஆய்வின் தலைப்பு : அரசு குழந்தைகள் நல மருத்துவமனையில் அனுமதிக்கப்பட்டுள்ள தலசிமியா குழந்தைகளுக்கு இதய மின் ஒலி வரைவியல் ஏற்படும் மாற்றங்களை பற்றிய ஆய்வு

1) எனக்கு தரப்பட்ட ஆராய்ச்சியில் பங்கு பெறுவோர்க்கான தகவல் படிவத்தை முழுவதுமாக படித்து புரிந்து கொண்டேன்.

2) ஆராய்ச்சியின் தன்மை முழுவதுமாகவும் விரிவாகவும் எடுத்துரைக்கப்பட்டது. எனது கேள்விகளுக்கு விடையளிக்கப்பட்டது.

3) ஆய்வாளர் என் உரிமைகளையும், பொறுப்புகளையும் நன்கு விளக்கினார்.

4) நான் எனது குழந்தை ஆய்வாளருக்கு முழு ஒத்துழைப்பு கொடுக்கவும், பரிசோதனை செய்து கொள்ளவும் அனுமதிக்கிறேன்.

5) எனது குழந்தை ஆராய்ச்சியில் பங்கேற்பதால் ஏற்படும் சாதக பாதகங்களை விளக்கப்பட்டன.

6) நான் எப்பொழுது வேண்டுமானாலும் எனது குழந்தையை இந்த ஆராய்ச்சியிலிருந்து விலக்கிக் கொள்ளலாம் என்று எனக்கு எடுத்துரைக்கப்பட்டது. அவ்வாறு விலகிக்கொள்வதால் குழந்தைக்கு அளிக்கப்படும் சிகிச்சையில் எந்த மாற்றமும் இருக்காது என அறிந்து கொண்டேன்.

7) இந்த ஆய்வில் என் குழந்தையிடமிருந்து பெறப்படும் மருத்துவ தகவலை ஆய்விதழிலோ, கருத்தரங்கிலோ வெளியிடுவதில் எனக்கு எந்தவித ஆட்சேபனையும் இல்லை.

8) அவ்வாறு வெளியிடப்படும்போது என் குழந்தையின் தன் அடையாளங்களை வெளியிடப்பட மாட்டாது என எனக்கு உறுதியளிக்கப்பட்டது.

9) எனக்கு இந்த ஆராய்ச்சி குறித்து எதுவும் சந்தேகம் இருந்தால் உடனே ஆராய்ச்சியாளரை கேட்டு தெளிவுப்படுத்திக் கொள்ளலாம் என தெரிவிக்கப்பட்டது.

10) இந்த ஒப்புதல் படிவத்தில் கையொப்பமிடுவதின் மூலம் இந்த படிவத்தில் உள்ளவை யாவும் எனக்கு தெளிவாக எடுத்துரைக்கப்பட்டு அதை நான் நன்கு புரிந்துக்கொண்டேன் என தெரிவித்துக்கொள்கிறேன்.

நோயாளியின் பெற்றோர் / பாதுகாவலர்

பெயர்:_____ கையொப்பம்:_____
தேதி:

ஆராய்ச்சியாளர்

பெயர்:_____ கையொப்பம்:_____

தேதி:

சாட்சி 1:

பெயர்:_____ கையொப்பம்:_____
தேதி:

சாட்சி 2:

பெயர்:_____ கையொப்பம்:_____
தேதி:

PROFORMA

STUDY OF SIGNIFICANCE OF ECHOCARDIOGRAPHY IN THALASSEMIA MAJOR/INTERMEDIA PATIENTS ATTENDING A TERTIARY CARE CENTRE, ICH, CHENNAI.

Serial Number: Ip No: Date:

1.Name: 2. Age: 3. Sex:

4. Residence:

5. Socioeconomic Status: (Modified Kuppuswamy Classf)

6. Consanguinity:

7.COMPLAINTS:

8.PAST HISTORY:

- Number of previous transfusions
- On chelation therapy: yes/no

9.FAMILY HISTORY:

ANTHROPOMETRY:

10. Weight: Expected Weight: Centile

11. Height: Expected Weight: Centile:

12. Body surface area:

GENERAL EXAMINATION

13. Pallor 14. icterus / lymphadenopathy

VITAL SIGNS

15. Pulse rate 16. Respiratory rate

17. Blood pressure 18. Temperature

SYSTEMIC EXAMINATION:

19. Cardiovascular system:

20. Abdomen: liver

spleen

21. Respiratory system:

22. Central Nervous system:

23. CBC: HB: PCV: TC: DC:

MCV: MCH: MCHC: RDW:

PLATELETS:

24. HB ELECTROPHORESIS:

25: SERUM FERRITIN:

26. CHEST- XRAY:

27. ECG:

27. ECHO:

MASTER CHART

name	age	sex	ip no	residence	ses	consanguinous	age at diagnosis	frequency	chelation	sibling	weight	< 3 PERCTILE
ashika	3	female	877016	rural	low	ncm	14 mon	monthly	yes	1 normal	14	N
swetha	11	female	877023	rural	low	cm	5 mon	monthly	yes	1 normal	22	LESS
vishwa	6	male	875387	rural	low	ncm	6 mon	monthly	yes	nil	15	LESS
meenatchi	3.6	female	877342	rural	low	ncm	5 mon	monthly	yes	2 normal	15	N
yogeshwari	5	female	866447	urban	low	cm	11 mon	monthly	yes	1 normal	15	N
dhanush	9	male	862492	urban	low	ncm	5 mon	monthly	yes	1 normal	24	n
isha	9	female	862497	urban	low	ncm	7 month	monthly	yes	2 normal	23	n
sabarivasan	5	male	876510	rural	low	cm	5 months	monthly	yes	1 normal	15	N
regan	3	male	876528	urban	low	ncm	8 month	monthly	yes	1 normal	11	LESS
dharamraj	4	male	872723	urban	low	ncm	4 months	monthly	yes	nil	12	N
lithika	5	female	874638	urban	low	cm	3 months	monthly	yes	1 normal	17	N
subhash	8	male	874111	urban	low	cm	3 years	3 months	yes	1 affected	20	n
madhavan	7	male	874112	urban	low	cm	3 years	3 months	yes	1 affected	18	n
prashanth	12	male	875835	rural	low	cm	7 month	monthly	yes	1 normal	32	n
nisha	8	female	876166	rural	low	cm	7 month	monthly	yes	nil	18	n
veeramani	12	male	875701	rural	low	cm	18 months	monthly	yes	2 normal	27	n
jeyalakshmi	8	female	850147	rural	low	cm	5 months	monthly	yes	2 normal	17	n
lokesh	10	male	862467	urban	low	ncm	6 months	monthly	yes	1 normal	22	n
vijayarasu	4	male	860458	urban	low	cm	6 months	monthly	yes	1 normal	12	N
kokila	9	female	800948	rural	low	ncm	2 years	2 months	yes	1 normal	20	n
suresh	4	male	865950	rural	low	ncm	1 years	2 months	yes	nil	14	N
asraf	2	male	850142	urban	low	ncm	6 months	monthly	yes	1 normal	12	N
abhisha	7	female	866416	rural	low	cm	6 months	monthly	yes	1 normal	15	LESS
alfara	2	female	875029	rural	low	ncm	4 months	months	yes	1 died	12	N
abu bakkar	3	male	878512	urban	low	ncm	6 months	monthly	yes	1 normal	12	N
naveen	2	male	875983	urban	low	ncm	1 years	monthly	yes	1 normal	11	N
neelavanan	3	male	875695	rural	low	cm	3 months	monthly	yes	2 dead	13	N
pugalandi	8	male	877022	rural	low	cm	1 years	monthly	yes	1 dead	20	n
thoufik	9	male	873771	urban	low	ncm	11 month	monthly	yes	nil	20	LESS
diwakar	7	male	877018	rural	low	ncm	7 month	monthly	yes	1 affected	18	n
abhirami	5	female	877019	rural	low	ncm	6 months	monthly	yes	1 affected	15	n
prithika	5	female	876748	rural	low	cm	9 months	monthly	yes	1 normal	12	LESS
harish	3	male	872532	rural	low	ncm	1 years	2 months	yes	1 normal	11	N
deep mondol	7	male	876742	rural	low	ncm	6 months	monthly	yes	1 normal	15	LESS
tejas	2	male	876628	rural	low	ncm	6 months	monthly	yes	nil	10	N
dharmaraj	4	male	871213	urban	low	ncm	4 months	montly	yes	nil	12	N
gugan	2	male	876444	rural	low	cm	6 months	monthly	yes	nil	11	N
lokesh	4	male	874379	urban	low	ncm	7 month	monthly	yes	1 normal	14	N
thaita parveen	3	female	849807	urban	low	ncm	7 month	2 months	yes	1 dead	12	N
allen	9	male	867458	rural	low	cm	6 monhs	monthly	yes	1 normal	22	n
raghul	6	male	862081	urban	low	ncm	4 months	monthly	yes	1 normal	16	LESS
ansari khan	4	male	875602	urban	low	ncm	2 years	2 months	yes	nil	14	N
vimal	3	male	876921	urban	low	cm	2 years	monthly	yes	2 dead	11	N
ramya	11	female	876797	rural	low	cm	1 years	monthly	yes	2 dead	20	LESS
raghava	3	male	863760	rural	low	ncm	5 months	monthly	yes	nil	12	N
anbulagan	6	male	845979	rural	low	ncm	6 months	monthly	yes	1 normal	19	n
jeeva	3	male	877362	rural	low	ncm	6 months	monthly	yes	1 normal	13	N
puniya	7	female	869112	rural	low	cm	6 months	monthly	yes	nil	20	n
keerthi	5	female	873674	urban	low	cm	11 months	monthly	yes	1 normal	15	LESS
devadarshan	3	male	874888	urban	low	cm	8 month	monthly	yes	1 normal	11	N
hemavathy	9	female	877456	urban	low	cm	7 month	monthly	yes	1 normal	17	LESS
nivedha	6	female	877462	rural	low	cm	2 years	monthly	yes	nil	17	n
venkatesh	4	male	872417	rural	low	ncm	6months	monthly	yes	I normal	15	n
pooja	3	female	875192	rural	low	ncm	6 months	monthly	yes	nil	13	n

height	< 2nd SD	< 3 rd SD	CENTILE	BSA	pallor	HR	RR	BP	temperature	CVS	RS	liver	spleen	Hb	MCV	MCH	Platelets	Hb electrophoresis	chest x ray
90	NO	NO	10 th	0.6	yes	N	N	N	N	n	N	2 cm	3 cm	7	75	25	2.2 lakhs	major	cardiomegaly
134	NO	NO	Normal	0.9	yes	N	N	N	N	N	N	2cm	4 cm	7.7	75	25	1.8 lakhs	major	cardiomegay
100	YES	YES	less than 3rd	0.65	yes	N	N	N	N	n	N	5cm	6 cm	6	77	25	1.2	majpr	NORMAL
96	NO	NO	30 th	0.64	yes	tachy	N	N	N	N	N	2cm	1cm	7	76	25	2.9 lakhs	major	NORMAL
96	YES	NO	less than 3rd	0.64	yes	tachy	N	N	N	N	N	2m	1cm	7	77	25	2.4 lakhs	major	NORMAL
125	NO	NO	10 th	0.9	yes	tachy	N	N	N	N	N	2 cm	6 cm	6	75	25	2.5 lakhs	major	cardiomegaly
121	NO	NO	10 th	0.88	yes	tachy	N	N	N	N	N	3cm	4 cm	8.6	88	26	2 lakhs	major	cardiomegaly
97	NO	NO	less than 3rd	0.64	yes	tachy	N	N	N	N	N	3cm	4 cm	6	82	25	1.2 lakhs	major	cardiomagaly
91	NO	NO	10 th	0.54	yes	tachy	N	N	N	N	N	3 cm	5cm	7	76	25	1.9 lakhs	major	cardiomegaly
97	NO	NO	Normal	0.57	yes	tachy	N	N	N	N	N	3cm	2 cm	10	78	38	2.6 lakhs	major	cardiomegaly
98	YES	NO	less than 3rd	0.7	yes	tachy	N	N	N	N	N	2cm	2cm	7.6	77	26	1.4 lakhs	major	NORMAL
105	YES	YES	less than 3rd	0.78	yes	N	N	N	N	N	N	2 cm	5cm	10	82	28	2.7 lakhs	intermedia	cardiomegaly
102	YES	YES	less than 3rd	0.72	yes	N	N	N	N	N	N	5cm	6 cm	8	77	25	2 lakhs	intermedia	NORMAL
145	NO	NO	Normal	0.7	yes	N	N	N	N	N	N	2 cm	4 cm	6	73	25	1.3 lakhs	major	cardiomegaly
103	YES	YES	less than 3rd	0.7	yes	N	N	N	N	N	N	2cm	3 cm	7	77	25	1.8 lakhs	major	NORMAL
130	YES	YES	10 th	0.97	yes	N	N	N	N	N	N	2cm	4 cm	6.5	70	22	2.3 lakhs	major	cardiomegaly
105	YES	YES	less than 3rd	0.7	yes	N	N	N	N	N	N	2 cm	3 cm	8.9	79	26	3.43 lakhs	major	cardiomegaly
127	NO	NO	5 th	0.88	yes	N	N	N	N	N	N	2 cm	3 cm	7	70	23	1.5 lakhs	major	cardiomegaly
97	NO	NO	10 th	0.57	yes	tachy	N	N	N	N	N	3cm	6 cm	6	70	24	1 lakh	major	cardiomegaly
115	YES	YES	less than 3rd	0.8	yes	tachy	N	N	N	N	N	3 cm	10 cm	6.5	67	22	1.64 lakh	intermedia	cardiomegaly
99	NO	NO	Normal	0.62	yes	N	N	N	N	N	N	2 cm	4cm	6	64	24	1.4 lakhs	intermedia	cardiomegaly
86	NO	NO	Normal	0.52	yes	tachy	N	N	N	N	N	2cm	3 cm	6.2	78	27	3 lakhs	major	NORMAL
109	YES	YES	less than 3rd	0.66	yes	tachy	N	N	N	N	N	2 cm	3 cm	7	78	25	1.8 lakhs	major	NORMAL
87	NO	NO	Normal	0.52	yes	tachy	N	N	N	N	N	2 cm	5 cm	8.5	78	26	2 .2 lakhs	major	cardiomegaly
90	NO	NO	Normal	0.55	yes	tachy	N	N	N	N	N	2 cm	3 cm	7	75	25	3 lakhs	major	NORMAL
85	NO	NO	Normal	0.52	yes	N	N	N	N	N	N	4cm	5 cm	5.6	67	22	1,2 lakhs	major	NORMAL
86	YES	YES	less than 3rd	0.55	yes	tachy	N	N	N	N	N	5 cm	5 cm	6.5	72	24	2 lakhs	major	cardiomegaly
120	NO	NO	10 th	0.82	yes	N	N	N	N	N	N	3 cm	3 cm	6.5	75	25	2.3 lakhs	major	NORMAL
122	YES	YES	less than 3rd	0.81	yes	tachy	N	N	N	N	N	3 cm	4 cm	7.4	75	25	2.5 lakhs	major	cardiomegaly
98	YES	YES	less than 3rd	0.72	yes	tachy	N	N	N	N	N	2 cm	7 cm	7	76	25	2 lakhs	major	NORMAL
117	NO	NO	Normal	0.69	yes	N	N	N	N	N	N	6 cm	7 cm	6.5	72	24	1.4 lakhs	major	NORMAL
112	NO	NO	Normal	0.64	yes	N	N	N	N	N	N	1 cm	3 cm	6.8	75	25	2.2 lakhs	major	NORMAL
91	NO	NO	10 th	0.54	yes	N	N	N	N	N	N	2 cm	3 cm	6.7	102	31	3.16 lakhs	intermedia	cardiomegaly
107	YES	YES	less than 3rd	0.66	yes	tachy	N	n	N	N	N	3cm	4 cm	7.2	77	25	2.9 lakhs	major	cardiomegaly
90	NO	NO	Normal	0.51	yes	N	N	N	N	N	N	2cm	2 cm	8	79	30	5 lakhs	major	cardiomegaly
100	NO	NO	Normal	0.59	yes	tachy	N	N	N	N	N	2 cm	3 cm	10	78	38	2.6 lakhs	major	cardiomegaly
91	NO	NO	Normal	0.54	yes	tachy	N	N	N	N	N	2 cm	4 cm	7	75	25	3.4 lakhs	major	NORMAL
110	NO	NO	Normal	0.66	yes	N	N	N	N	N	N	2 cm	3 cm	8.8	77	25	3.8 lakhs	major	cardiomegaly
106	NO	NO	Normal	0.59	yes	tachy	N	N	N	N	N	2 cm	3 cm	9	80	30	2.8 lakhs	intermedia	NORMAL
125	NO	NO	Normal	0.89	yes	N	N	N	N	N	N	2 cm	5 cm	7	75	24	1.6 lakhs	major	cardiomegaly
110	NO	NO	Normal	0.7	yes	N	N	N	N	N	N	3 cm	4 cm	7.8	77	26	2 lakhs	major	cardiomegaly
105	NO	NO	Normal	0.64	yes	tachy	N	N	N	N	N	2 cm	4cm	7.5	77	25	2.6 lakhs	intermadia	cardiomegaly
92	NO	NO	Normal	0.54	yes	tachy	N	N	N	N	N	2 cm	1 cm	7.4	76	23	2 lakhs	major	cardiomegaly
122	YES	YES	less than 3rd	0.81	yes	N	N	N	N	N	N	2cm	4 cm	10	80	30	2.7 lakhs	major	cardiomegaly
95	YES	YES	less than 3rd	0.58	yes	tachy	N	N	N	N	N	1.5 cm	3 cm	8.8	67	28	3.2 lakhs	major	NORMAL
116	NO	NO	Normal	0.79	yes	N	N	N	N	N	N	2 cm	3 cm	7	75	25	2.3 lakhs	major	cardiomegaly
107	NO	NO	Normal	0.62	yes	N	N	N	N	N	N	2cm	4 cm	7	80	26	1.38 lakhs	major	NORMAL
118	NO	NO	Normal	0.81	yes	tachy	N	N	N	N	N	3 cm	4 cm	6.5	75	25	1.8 lakhs	major	cardiomegaly
105	NO	NO	Normal	0.66	yes	tachy	N	N	N	N	N	3 cm	6 cm	6.5	78	25	1.68 lakhs	major	cardiomegaly
90	NO	NO	10 th	0.54	yes	tachy	N	N	N	N	N	2cm	4 cm	6.7	80	27	2.7 lakhs	major	cardiomegaly
117	YES	NO	Normal	0.74	yes	N	N	N	N	N	N	2cm	3cm	8.9	84	30	3.8 lakhs	major	cardiomegaly
100	NO	YES	less than 3rd	0.7	yes	N	N	N	N	N	N	2cm	5cm	8	81	31	2 lakhs	major	cardiomegaly
96	YES	YES	less than 3rd	0.62	yes	tachy	N	N	N	N	N	2 cm	4 cm	6.9	77	25	1. 9 lakhs	major	cardiomegaly
92	NO	NO	10th	0.6	yes	tachy	N	N	N	N	N	1cm	4 cm	7	78	25	2 lakhs	major	cardiomegaly

ecg	RVH	LVH	QT_c interval	echo	ferritin	tr	pht	lv mass	lvm/m2	lvmass >95centile	EF (NORMAL 56 % TO 78 %)	% fs (28-44)	trv	pericardial effusion	total no of transfusions
Normal	NIL	NIL	N	ab	1271	n	mild	47	78.3	INCREASED	67	36	2.6	no	22
ab	+	+	N	ab	1750	trivial	no	82	91.1	INCREASED	67	37	2.5	no	127
Normal	NIL	NIL	N	normal	290	N	no	45	69.2	NORMAL	61	32	2.3	no	66
Normal	NIL	NIL	N	normal	420	trivial	no	37	52.8	NORMAL	70	41	2.4	no	43
Normal	NIL	NIL	N	ab	2478	mild	mild	160	250	INCREASED	67	37	2.8	no	49
ab	+	+	N	ab	2000	trivial	no	137	152.2	INCREASED	74	43	2.3	no	103
ab	NIL	+	N	ab	1752	trivial	no	80.1	91	INCREASED	77	45	2.2	no	101
Normal	NIL	+	N	ab	5750	mild	mild	39.4	61.5	NORMAL	63	32	2.9	no	55
Normal	NIL	NIL	N	ab	2000	mild	mild	174	322.2	INCREASED	71	40	2.8	no	32
Normal	NIL	NIL	N	ab	1913	trivial	mild	64	106.6	INCREASED	75	41	2.4	no	44
Normal	NIL	NIL	N	ab	2135	n	no	78	111.4	INCREASED	74	43	2.1	no	57
ab	NIL	+	N	ab	961	mild	mild	98	125.64	INCREASED	70	42	2.4	no	20
Normal	NIL	NIL	N	normal	215	n	no	49	68	NORMAL	70	58	2	no	16
ab	NIL	+	N	ab	1152	N	NO	163	232	INCREASED	70	36	2.1	no	71
Normal	NIL	NIL	N	normal	1980	N	NO	54.2	77.4	NORMAL	67	36	1.9	no	89
ab	NIL	+	N	ab	2942	mild	no	210	216	INCREASED	68	38	2.5	no	126
ab	NIL	+	N	ab	7192	N	no	88	125.7	INCREASED	N	N	2.5	no	91
ab	NIL	+	N	ab	1002	N	no	102	115.9	INCREASED	N	N	2.2	no	114
ab	NIL	+	N	ab	6191	N	no	77	128	INCREASED	70	41	2.5	no	42
Normal	NIL	NIL	N	ab	400	mild	mild	180	225	INCREASED	55	28	2.9	no	42
ab	+	NIL	N	ab	2188	n	no	220	314.2	INCREASED	71	40	2.7	no	18
Normal	NIL	NIL	N	normal	1183	mild	no	43.6	71.6	NORMAL	66	39	2.5	no	18
Normal	NIL	NIL	N	ab	2878	mild	no	131	187	INCREASED	66	39	2.5	plus	78
Normal	NIL	NIL	N	ab	512	mild	no	52.1	100	INCREASED	64	34	2.6	no	16
Normal	NIL	NIL	N	ab	1822	trivial	no	47	85.4	INCREASED	70	41	2.7	no	30
Normal	NIL	NIL	N	ab	1463	mild	mild	29	52.7	NORMAL	62	33	2.7	plus	12
ab	+	NIL	N	normal	675	n	no	33.3	41	NORMAL	70	41	2.1	no	33
Normal	NIL	NIL	N	ab	4277	n	no	103	125.6	INCREASED	63	34	2.1	no	84
ab	NIL	+	N	ab	7610	mild	no	77	95.06	INCREASED	73	35	2.6	no	97
Normal	NIL	NIL	N	normal	1086	n	no	57	79.1	INCREASED	64	34	2.1	no	77
Normal	NIL	NIL	N	ab	2124	mild	mild	53	76.8	INCREASED	70	39	2.6	no	54
ab	NIL	+	N	ab	3928	trivial	no	58.8	91.8	INCREASED	76	44	2.4	no	51
Normal	NIL	NIL	N	normal	5382	n	no	30.3	56.1	INCREASED	73	41	2.4	no	12
ab	+	+	N	ab	6750	trivial	no	61.22	92.7	INCREASED	80	47	2.4	no	78
ab	NIL	+	N	ab	658	n	no	49	96.7	INCREASED	70	38	2.3	no	18
ab	NIL	+	N	ab	1913	N	no	88	149.1	INCREASED	78	46	2.4	no	44
Normal	NIL	NIL	N	normal	1998	trivial	no	19.28	35.1	NORMAL	75	40	2.6	no	18
Normal	NIL	NIL	N	normal	1986	n	no	42	60	INCREASED	75	43	2.3	no	41
Normal	NIL	NIL	N	normal	305	n	no	27	45	NORMAL	80	48	2.3	no	15
Normal	NIL	NIL	N	normal	915	trivial	no	71.8	80.89	INCREASED	74	43	2.5	no	102
Normal	NIL	NIL	N	normal	976	n	no	64	91.4	INCREASED	69	38	2.3	no	68
Normal	NIL	NIL	N	ab	5910	mild	mild	60.13	93.9	INCREASED	63	32	2.6	no	12
Normal	NIL	NIL	N	normal	2011	trivial	no	52.31	96.8	INCREASED	73	41	2.6	no	12
Normal	NIL	NIL	N	N	3959	n	no	66.76	82.4	INCREASED	71	40	2.1	no	120
Normal	NIL	NIL	N	normal	569	trivial	no	30.12	50	NORMAL	70	38.6	2.5	no	31
ab	NIL	+	N	N	4279	N	no	91.34	114.1	INCREASED	72	40	2.4	no	66
Normal	NIL	NIL	N	normal	1578	N	no	28.64	47.6	NORMAL	75	40	2.2	no	30
ab	NIL	+	N	ab	3321	trivial	mild	90.03	111.1	INCREASED	76	44	2.6	no	78
Normal	NIL	NIL	N	ab	2505	N	no	56.46	76.3	INCREASED	82	49	2.1	no	49
Normal	NIL	NIL	N	ab	9843	N	no	98.3	163.3	INCREASED	63	34	2.2	no	28
Normal	NIL	NIL	N	ab	1124	trivial	mild	77.01	104	INCREASED	80	48	3.1	no	101
Normal	NIL	NIL	N	ab	5813	mild	mild	56.12	80.17	INCREASED	63	34	2.8	no	48
ab	nil	plus	N	ab	5917	n	no	44.8	72.2	INCREASED	63	33	2.3	no	42
Normal	nil	nil	N	ab	600	n	no	38.9	64.3	INCREASED	62	40	2.2	no	30